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THE AMERICAN HEART JOURNAL

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The American Heart Journal

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Original Communications

THE RÔLE OF SYPHILIS IN THE ETIOLOGY OF ANGINA PECTORIS, CORONARY ARTERIOSCLEROSIS AND THROMBOSIS, AND OF SUDDEN CARDIAC DEATH*

ALDRED SCOTT WARTHIN, M.D.,
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THE rôle played by syphilis in the etiology of angina pectoris, coronary sclerosis and thrombosis, and of cardiac infarction has never been clearly evaluated; and varying opinions have been held by clinicians as to its importance in the production of these conditions. The most recent writers, as Levine, believe that syphilis is rarely an underlying factor in the causation of coronary thrombosis. In only three of Levine's eighty-nine cases in which a Wassermann reaction was done was there a positive reaction, and in one other case with a negative reaction, there was a history of a primary infection. From this it would appear that only 4.5 per cent of his patients were syphilitic, and it does not necessarily follow that in these cases the syphilis was the etiologic factor in the production of coronary thrombosis. In one case only, a patient only thirty-six years old, the youngest in his series, did this seem likely. In the other cases the syphilis may well have been coincidental. Levine decides that coronary thrombosis and myocardial infarction are rarely caused by syphilis. However, in Levine's cases the diagnoses were chiefly clinical and gross pathological. In only forty-six of the cases were autopsies done, and the microscopic diagnosis of syphilis does not seem to have been considered. It is possible that microscopic criteria for the diagnosis of syphilis might have increased the percentage of syphilities in his material. In thirteen autopsies on patients dying of coronary disease reported by W. J. Stone, microscopical examination showed syphilitic periarteritis in two cases. In eighty-six autopsies of coronary sclerosis, Willius and Brown found syphilis of the aorta in 19 per cent.

*Read before the Association of American Physicians, Atlantic City, May 6, 1930.
From the Department of Pathology, University of Michigan, Ann Arbor, Mich.

It was decided to approach the solution of this question from the standpoint of the microscopic diagnosis of syphilitic lesions, as this has never been carried out before on any large series of cases. In the twenty years, 1909 to 1929, there were in the Pathological Laboratory of the University of Michigan, 1675 autopsies on individuals over twenty-five years of age. Of this number, there were 408 males and 86 females that showed the microscopic lesions of active latent syphilis. These lesions consisted of characteristic perivascular infiltrations of lymphocytes and plasma cells around small vessels, with obliteration of the arterioles and resultant fibrosis. In about 50 per cent of cases the presence of spirocheta pallida was demonstrated in this lesion. The highest incidence of these lesions was found in the aorta; 97.6 per cent of cases for the first decade, 1909 to 1919; in 86.3 per cent of cases for the second decade, 1919 to 1929.

TABLE I*

YEAR	TOTAL AUTOPSIES OVER 25 YEARS	MALES WITH LATENT SYPHILIS	FEMALES WITH LATENT SYPHILIS
1910	11	1	0
1911	20	3	1
1912	26	5	1
1913	24	8	3
1914	31	10	0
1915	35	17	4
1916	48	19	3
1917	90	36	9
1918	40	16	3
1919	61	20	3
1920	94	26	4
1921	84	22	7
1922	95	18	5
1923	116	23	8
1924	133	25	6
1925	137	33	6
1926	199	48	8
1927	203	33	5
1928	177	32	8
1929	51	13	2
	1675	408	86

*Cases of latent syphilis occurring in autopsies on adults over twenty-five years of age, in the Pathological Laboratory of the University of Michigan, during the last twenty years.

The distribution of these microscopic lesions of latent syphilis in the various organs and tissues is shown for the first decade in Table II, and for the second decade in Table III. These percentages show the preponderance of the aortic lesions over all others, followed by the meninges, testis and heart.

The microscopical study of the heart and coronary vessels shows the following: In 169 cases of syphilis (1909 to 1919) there were fifty-three cases of coronary sclerosis without thrombosis, nine cases of syphilitic disease of the coronaries, one case of coronary thrombosis

and sclerosis, and no case with a clinical history of angina pectoris. In this decade there were thirteen cases of sudden death without previous anginal history, in the 169 cases of syphilis. Nine of these cases showed marked coronary sclerosis without evidence of syphilitic coronary involvement; four cases showed the lesions of coronary sclerosis and syphilis. In nine of these cases there was a diffuse interstitial myocarditis of the syphilitic type; in four only was there a microscopic picture of myocardial infarction.

TABLE II*

TISSUE	TOTAL EXAMINED	NO. SYPHILITIC	PER CENT SYPHILITIC	NO. SUSPICIOUS
Spinal cord	8	4	50.0	
Brain	36	19	52.78	
Meninges	40	39	97.5	
Aorta	163	159 (6 aneurysms)	97.6	4
Heart	169	113 (3 aneurysms)	66.9	5
Liver	165	46 (4 gummas)	27.8	13
Adrenals	153	47	30.7	1
Pancreas	163	72	44.1	4
Testis	137	118	86.1	5

*Distribution of Lesions of Latent Syphilis in 169 Cases of Syphilis (142 males, 27 females), in 368 autopsies over 25 years of age, 1909-1919. 43.7 per cent latent syphilitics.

TABLE III*

TISSUE	TOTAL EXAMINED	NO. SYPHILITIC	PER CENT SYPHILITIC	NO. SUSPICIOUS
Spinal cord	60	27	45.0	1
Brain	198	71 (4 gummas)	39.9	2
Meninges	202	168 (2 gummas)	83.2	0
Aorta	327	282 (29 aneurysms)	86.3	7
Heart	330	216 (2 gummas)	65.5	7
Liver	328	102 (12 gummas)	31.4	4
Adrenals	320	145 (1 gumma)	45.3	2
Pancreas	328	98 (2 gummas)	29.8	0
Testis	264	203	76.5	10

*Distribution of Lesions of Latent Syphilis in 332 Cases of Syphilis (275 males, 57 females) in 1289 autopsies over 25 years of age, 1919-1929. 25.7 per cent latent syphilitics.

In this material were two gummas of lung, one of pulmonary artery, two of spleen, two of bone, one of thyroid, two of skin.

TABLE IV

1909 TO 1919. 386 AUTOPSIES IN PATIENTS OVER 25 YEARS OF AGE, WITH 169 CASES OF SYPHILIS SHOWING

Coronary sclerosis	53
Coronary syphilis	9
Coronary thrombosis and sclerosis	1
Angina pectoris	0
Sudden death	13
Sudden death with coronary sclerosis	9
Sudden death with coronary syphilis	4
Sudden death with myocardial infarction	4
Sudden death with diffuse myocarditis	9
Myocardial infarction with coronary sclerosis	4
Myocardial infarction with coronary syphilis	0

In the decade 1919 to 1929, in the 332 cases of latent syphilis there were 172 cases of coronary sclerosis, and 55 cases showing syphilitic lesions of the coronaries, including one case of gummatous coronary arteritis. In this group there were five cases of coronary occlusion by thrombosis; four of these were associated with coronary sclerosis alone, and one with syphilis of the coronary. There were six cases of angina pectoris in this group; five of these were associated with coronary sclerosis alone, one with syphilis of the coronary main branches. There were twenty-five cases of sudden death in this decade in the syphilitic group; in thirteen of these the coronaries showed arteriosclerosis alone; in twelve cases there were lesions of syphilis in the coronaries, six of these showed both syphilis and sclerosis. Eleven of the cases of sudden death showed myocardial infarction; fourteen showed no infarction, but the picture of a chronic diffuse interstitial myocarditis with fibrosis. Five of the cases of myocardial infarction were associated with occlusion due to coronary sclerosis alone; six were associated with both sclerosis and lesions of syphilis.

TABLE V

1919 TO 1929. 1289 AUTOPSIES IN PATIENTS OVER 25 YEARS OF AGE, WITH 332 CASES OF SYPHILIS SHOWING

Coronary sclerosis	172
Coronary syphilis (1 gummatous arteritis)	55
Coronary thrombosis	5
Coronary thrombosis with coronary sclerosis	4
Coronary thrombosis with coronary syphilis	1
Angina pectoris	6
Sudden death	25
Sudden death with coronary sclerosis	13
Sudden death with coronary syphilis (With both sclerosis and syphilis, 6)	12
Sudden death with myocardial infarction	11
Sudden death with diffuse myocarditis	14
Myocardial infarcts with coronary sclerosis	5
Myocardial infarcts with coronary syphilis	0
Myocardial infarcts with sclerosis and syphilis	6

Coronary Syphilis.—Syphilis of the coronaries involves most frequently the smallest intermuscular branches; only rarely are the main divisions the seat of active syphilitic lesions. In the latter the process is usually of the nature of a periarteritis, the small vessels of the adventitia showing perivascular infiltrations and fibrosis, resulting eventually in obliteration. Sclerosis of the intima invariably results, and syphilis must be regarded as one of the causes of coronary sclerosis, as it is of aortic. As aortic syphilis is always associated with coronary syphilis, the mouths of the coronaries may show the most marked sclerosis; in some cases they may be occluded by this process. In severe aortic syphilis this involvement of the coronaries may be limited to the first few millimeters, rarely more than 1 to 2 centimeters, of the main coronary. In our experience this occlusion of the coronary mouths

associated with syphilis is due chiefly to the secondary sclerosis produced by the syphilitic process, and rarely by active syphilitic infiltration or proliferations, which are present about the vasa vasorum in the neighboring aortic wall, and about the small nutrient perivascular branches of the main coronary. In only one of our cases did thrombosis occur in the partially occluded mouth of the coronary. An active proliferating endarteritis due to, or associated with, active syphilis is relatively rare in the larger branches of the coronaries. Gummatous arteritis was found in one very active case of syphilitic aortitis and myocarditis. In one case only was the coronary thrombosis directly associated with an active syphilis of the coronary vessel; in four other cases the thrombosis was due to the secondary coronary sclerosis asso-

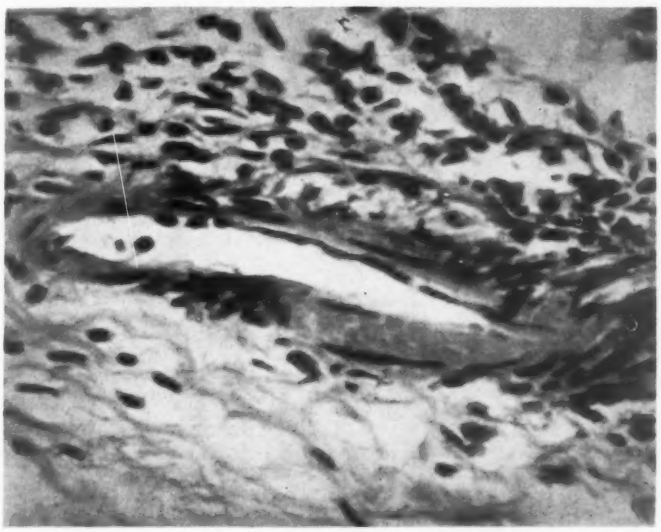

Fig. 1.—Active syphilitic perivascular infiltration of small subepicardial coronary vessel.

ciated with the syphilitic process. In all of the cases of acquired syphilis with the exception of two, the syphilitic lesions were chiefly about the descending branch of the left coronary. Involvement of the right coronary and its branches is rare in acquired syphilis, although more common in cases of congenital origin. Myocardial infarction is but extremely rarely the result of a pure syphilitic involvement of the coronary vessels; in the great majority of cases the infarction is caused by occlusion by the atherosclerotic obliteration of the lumen, with or without thrombosis. Syphilis of the smaller branches of the coronaries leads to a slow atrophy and fibrosis of the myocardium, but rarely does it produce an anemic necrosis of the muscle. If cardiac infarction is the essential pathological condition underlying angina pectoris, as it would seem to be in our cases, this failure of syphilis to produce infarc-

tion of the muscle would account for the rarity of an angina pectoris history in our cases of active coronary syphilis without secondary sclerosis.

When we compare the nonsyphilitic cases coming to autopsy during the same two decades, we find that in 1174 nonsyphilitic autopsies there were 412 cases of coronary sclerosis, with six cases of well-defined clinical angina pectoris, eight cases of coronary thrombosis and eight cases of myocardial infarction. In two cases sudden death from coronary thrombosis and myocardial infarction occurred without a history of angina.

TABLE VI*

PERIOD	NO. AUTOPSIES	CORONARY SCLEROSIS	ANGINA	MYOCARDIAL INFARCTION	CORONARY THROMBOSIS
1909-1919	217	52	1	1	1
1919-1929	957	360	5	7	7

*Distribution of Coronary Sclerosis, Angina, Myocardial Infarction and Coronary Thrombosis in the Non-Syphilitic Autopsies in 20-year period, 1909-1929.

In Table VII the percentages of coronary sclerosis, angina, coronary thrombosis and myocardial infarction are compared for the two decades. For 1909 to 1919 the percentage of coronary sclerosis in the nonsyphilitic autopsies was 24 per cent, for the same decade it was 31 + per cent in the syphilitic autopsies. For the decade 1919 to 1929 the percentage of coronary sclerosis in nonsyphilitics was 38 per cent, in the syphilitic autopsies it was 52 per cent. The percentage of angina in the nonsyphilitic autopsies of 1909 to 1919 was 0.46 per cent, in the decade 1919 to 1929 it was 0.53 per cent. In the syphilitic cases there was no case of angina in 1909 to 1919; in 1919 to 1929 the percentage of angina cases was 1.8 per cent. In the decade 1909 to 1919, in the nonsyphilitic autopsies the percentage of cases of myocardial infarction was 0.46, for the decade 1919 to 1929 it was 0.74. In the syphilitic autopsies the percentage of myocardial infarction was 2.4 for the decade 1909 to 1919, and 3.3 for 1919 to 1929.

TABLE VII

PERCENTAGES IN NONSYPHILITICS

PERIOD	NO. AUTOPSIES	CORONARY SCLEROSIS	ANGINA	MYOCARDIAL INFARCTION	CORONARY THROMBOSIS
1909-1919	217	24%	0.46%	0.46%	0.46%
1919-1929	957	38%	0.53%	0.74%	0.74%
		PERCENTAGES IN SYPHILITICS			
1909-1919	169	31+%	0	2.4%	0.58%
1919-1929	332	52 %	1.8%	3.3%	1.5 %

The most important thing revealed by the comparison of these charts is the fact that coronary sclerosis, angina pectoris, coronary thrombosis and myocardial infarction have a higher rate of incidence in the syphilitic cases than in the nonsyphilitic. The significance of these

facts must be that syphilis predisposes to the production of coronary atherosclerosis with its attendant pathology. While coronary occlusion, thrombosis, myocardial infarction and angina pectoris are rarely the direct result of active syphilitic lesions of the coronaries, they all occur more frequently in the syphilitic, because of the more marked tendency possessed by the latter to develop severe grades of secondary atherosclerosis of aorta and coronary branches. Syphilis, therefore, secondarily and not primarily, is an important factor in the production of coronary disease and its concomitant angina pectoris.

Still more important is the relationship shown to exist between latent syphilis and sudden cardiac death, as given in Table VIII. Sudden death due to cardiac decompensation and dilatation was almost

TABLE VIII

RELATION OF SUDDEN DEATH TO CORONARY SCLEROSIS AND CORONARY SYPHILIS IN 501 CASES OF SYPHILIS IN YEARS 1909-1929

Sudden death with coronary sclerosis	22 cases
Sudden death with coronary syphilis	16 cases
Sudden death with coronary sclerosis and syphilis	6 cases
Sudden death with diffuse myocarditis	23 cases
Sudden death with myocardial infarction	15 cases
Sudden death with coronary thrombosis	6 cases
Sudden death with coronary thrombosis and sclerosis	5 cases
Sudden death with coronary thrombosis and syphilis	1 case

five times as frequent in our latent syphilitics as in the nonsyphilitics. Many of these cases were coroner's autopsies. This bears out the writer's contention as to the importance of cardiac involvement as the frequent cause of death in the syphilitic. Syphilis acts both primarily and secondarily upon the heart. As a secondary factor it plays a large part in the production of aortic and coronary sclerosis; as a primary factor it produces myocardial insufficiency through the slow production of an interstitial fibrosis. Twenty-three of our cases of sudden death showed this lesion alone. In every one of these cases evidence of latent syphilis of the myocardium was found on serial sections, in the form of an increase of stroma cells and localized collections of lymphocytes and plasma cells. Valvular lesions were not present in any one of these cases. We therefore conclude that:

1. Active syphilitic lesions of the larger coronary branches are infrequent. They rarely produce occlusion of the vessel, or lead to thrombosis or myocardial infarction.

2. Arteriosclerosis of the coronaries, coronary occlusion, coronary thrombosis, myocardial infarction and angina pectoris are more frequent in the latent syphilitic than in the nonsyphilitic. Syphilis predisposes secondarily to coronary and aortic sclerosis and their resultant cardiac pathology.

3. Sudden cardiac death was almost five times as frequent in the syphilitic as in the nonsyphilitic autopsies. In the majority of cases this was due to cardiac insufficiency and dilatation, resulting from a diffuse interstitial myocarditis of slight degree, leading eventually to fibrosis.

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THE PATHOGENESIS OF BROWN INDURATION OF THE LUNG*

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IN A PREVIOUS paper[1] I showed that brown induration of the lung results only from those forms of cardiac disorder that are accompanied by a hypertension of the pulmonary circuit. These are, in the order of frequency, mitral disease (especially mitral stenosis), emphysema, pleural adhesions, marked diminution in lung volume from whatever cause, certain cases of marked scoliosis, open ductus Botalli and communications between both sides of the heart. In uncomplicated aortic lesions, in which an increased pressure in the pulmonary circuit does not occur (except perhaps for a short period in the terminal stage of heart failure) I have failed to find brown induration.

Furthermore, such lesions are never found unless arteriosclerosis of the grosser trunks of the pulmonary artery is present. Indeed, arteriosclerosis of the pulmonary vessels is practically never found except when a condition causing hypertension of the pulmonary circulation is present; so that one may say that arteriosclerosis limited to the pulmonary artery is pathognomonic of hypertension of the pulmonary circulation. This relationship is furthermore definitely demonstrable in the utter independence in the incidence of arteriosclerosis of both greater and lesser circulations, and furnishes strong support for the thesis that arteriosclerosis is due to intravascular tension and to no other factor. The detailed reasoning whereby this conclusion was reached has been submitted.[2]

Associated with arteriosclerosis of the pulmonary arteries lesions of the capillaries are manifest that are pathognomonic of hypertension of the pulmonary circulation. Indeed, these lesions are so characteristic that they enable one by microscopic observation alone to diagnosticate unerringly gross arteriosclerosis of the pulmonary arteries. The development and senescence of these capillary changes dominate the pathogenesis of the pneumonia of heart disease, and it is for the elucidation of this thesis that this study is submitted.

Normally, the capillaries of the uninjected lung are hardly visible. Here and there one notes a narrow slit, usually containing a single red blood cell. The connective tissue wall of the alveolus is narrow, uniform in thickness, and, with the exception of an occasional bulge of the lining epithelium, the alveolar lining is smooth (Fig. 1).

*Read by title at the American Society of Pathologists and Bacteriologists, New York City, April, 1930.

In the earliest phases of the lesion, the alveolar wall appears beaded. The capillaries are distinctly dilated and the walls are thickened (Fig. 2). In cross-section the capillaries bulge into the alveolar space. In more advanced cases, the dilatation of the capillaries and the thickening of their walls become more pronounced so that the alveolar wall becomes much thicker than normal and the beaded appearance becomes more pronounced (Fig. 3). In this stage, one can already note a profound increase in the connective tissue content of the alveolar wall, this increase consisting almost entirely of the enormously thickened capillary walls. In the latter stage of this lesion, the connective

Fig. 1.—Section of normal lung.

tissue content of the alveolar wall becomes comparatively enormous (Fig. 4). The connective tissue is rather cellular, the wall is much thickened, and there is a corresponding narrowing of the alveolar space, accounting in a large measure for the diminution in vital capacity in heart disorders (Peabody[3]). In some areas hyalinization of the connective tissue is apparent. The capillaries in this stage have become to a great extent obliterated. In the terminal phases, the deposition of connective tissue in the alveolar wall is so great that the alveolar space becomes but a narrow chink, and the lining epithelium, as is the case in all sclerosing organs, reverts to the appearance of the embryonal lung. Capillaries are almost entirely absent, the only vessels persisting in these areas being the greatly sclerosed arterioles

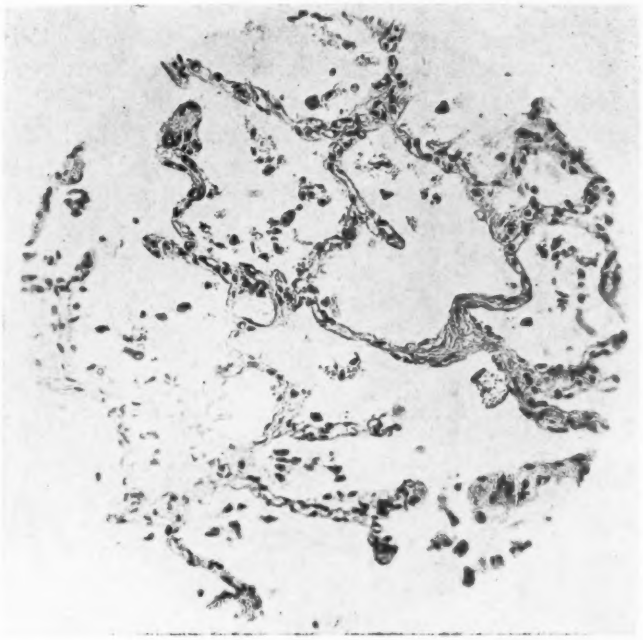

Fig. 2.—Early stage of arteriocapillary fibrosis of the lung consequent to mitral stenosis, showing dilated and thickened capillaries.

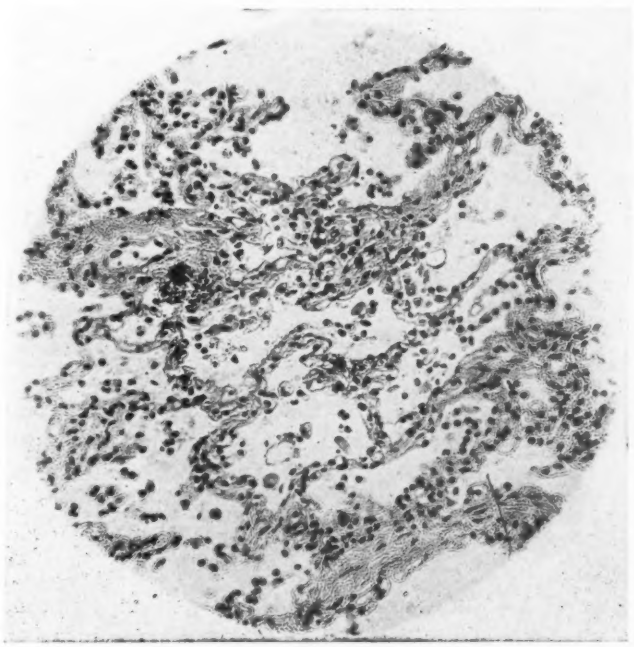

Fig. 3.—More advanced stage of arteriocapillary fibrosis of the lung, consequent to mitral stenosis.

and the grosser pulmonary vessels (Figs. 5 and 6). These changes are commonly seen in lungs that have been infarcted, but infarction is not the only cause of the increase in connective tissue. One can see in the immediate vicinity of such areas profoundly sclerotic arterioles with the lumen almost obliterated by intimal thickening. Unquestionably, therefore, diminution in the blood supply is in a large measure responsible for the connective tissue increase.

Grossly, the physical character of the lung corresponds to what we would expect from the microscopic appearance, varying from the suc-

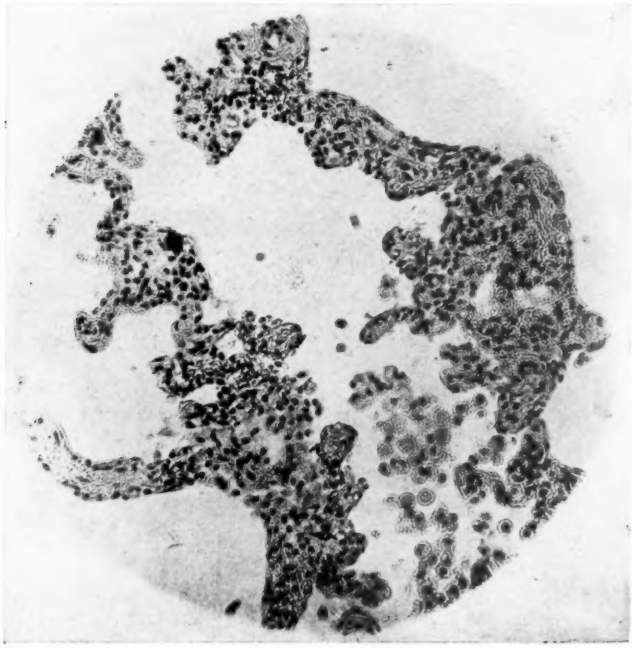

Fig. 4.—Advanced stage of arteriocapillary fibrosis of the lung, consequent to mitral stenosis.

culent, slightly tough organ of the earliest stage to the dense, carneous, fibrous and contracted lung of the terminal stage.

In summary, the capillary lesions of arteriosclerosis and hypertension of the pulmonary circulation represent a true arteriocapillary fibrosis, a term first employed by Gull and Sutton to connote corresponding changes in lesions of the greater circulation associated with hypertension.

In fact, the resemblance between the capillary lesions of the lung in hypertension of the pulmonary circulation and of the capillaries in hypertension of the greater circulation is striking; indeed, in almost every respect the appearances are identical. Both grossly and microscopically, the lesions in the lung represent the same stages as are

witnessed in the kidney in essential hypertension of the greater circulation. Just as in the kidney, where one can place in series organs that reveal only minimal changes in the early stage up to those of profound contraction in the terminal stage, so in the lung one can trace lesions that vary from the slightly carneous lung to that of the

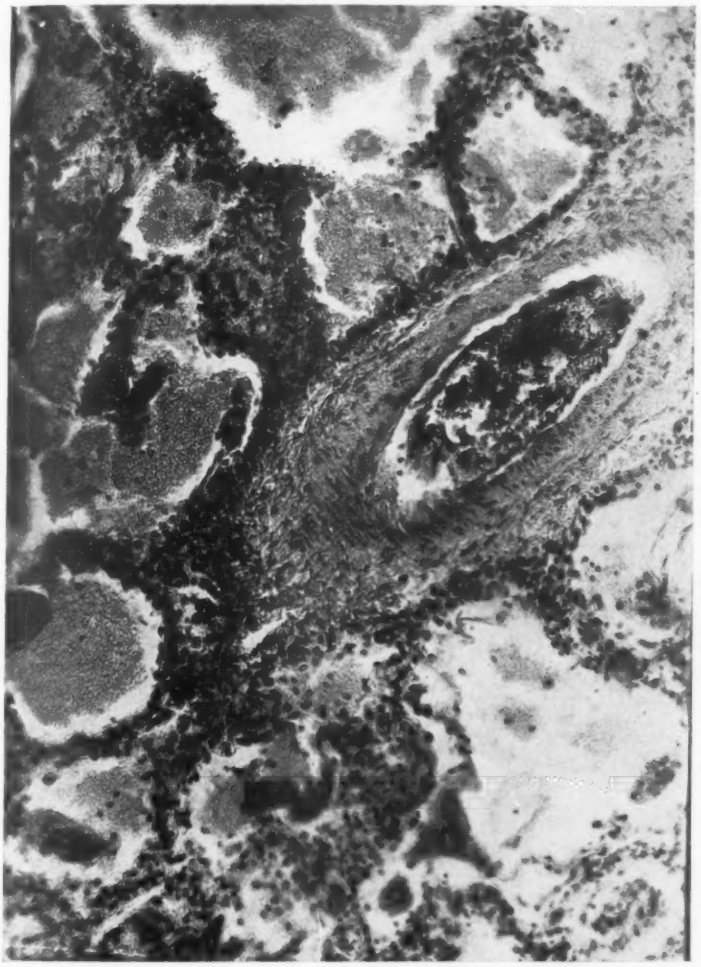

Fig. 5.—Advanced stage of arteriocapillary fibrosis of the lung, consequent to mitral stenosis.

advanced tissue transformation described above. Also, as in the kidney, the sclerosis is associated with, and, in the largest measure, consequent to partial and even complete cutting off of the blood supply by the sclerotic arterioles.

The pathological changes comprised under the term "pulmonary arteriocapillary fibrosis" are uniform, no matter where or how the resistance causing increased tension in the pulmonary circuit is pro-

duced. It is the same, therefore, whether the resistance arises in the mitral ring from a tight stenosis, or within the capillary bed, as in emphysema. Inasmuch as emphysema is in most instances a disease of advanced life, arteriosclerosis is present not only in the lesser but also in the greater circulation, in the latter as the result either of an

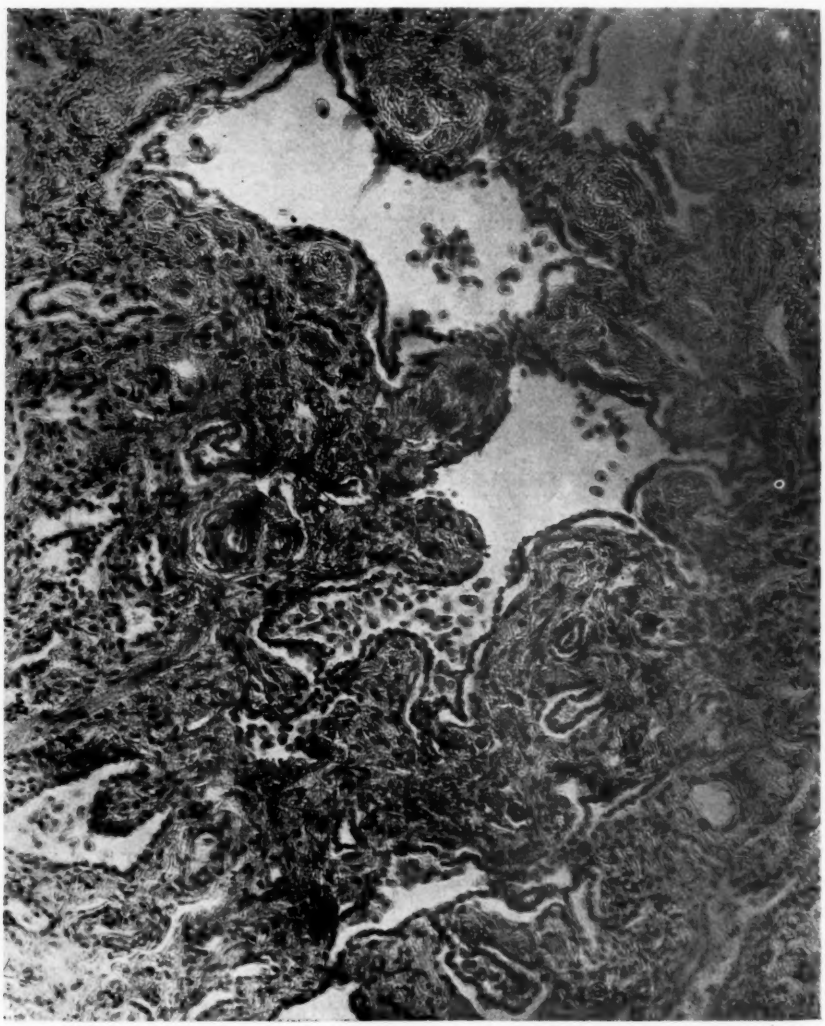

Fig. 6.—Final stage of arteriocapillary fibrosis (mitral stenosis) showing extensive fibrosis, sclerosis of the arterioles and reversion of the alveolar epithelium to the embryonal type.

associated hypertension or of decrescent change consequent on prolonged normal intravascular tension. It is, therefore, of considerable interest to report the findings in a case in which the emphysema occurred consequent to a bronchial asthma in an individual thirty-four

years of age, leading to a fatal issue from cardiac failure, a rare phenomenon in a person so young. The case is of especial importance for other reasons; because the arteriocapillary fibrosis was more advanced than any I have ever seen; because it revealed an unusual opportunity to study the lesions of bronchial asthma; and, finally, because the patient was followed clinically from almost the beginning of the disease to its termination.

CASE REPORT

D. H., aged 28 years, when seen by me in 1923 gave a history of having suffered from bronchial asthma for two and a half years. There was no history of asthma or any of the allergic diseases in her family. For four days there had been cough with fever. She had a wheezing dyspnea, and there were sibilant and sonorous râles throughout both lungs; there were dullness and diminished breathing at the right base with a few moist râles. The breathing was diminished also in the right upper lobe. The spleen was palpable. The blood pressure was 140/80 mm. Hemoglobin 95 per cent, red blood cells 4,750,000, leucocytes 6,100, polymorphonuclears 80 per cent, lymphocytes 19 per cent, monocytes 1 per cent. The sputum showed a number of Curschmann's spirals and some elastic tissue, but no tubercle bacilli. Culture of the sputum demonstrated anhemolytic and hemolytic streptococci and Micrococcus catarrhalis. Blood Wassermann reaction negative. Roentgenograms showed a pneumonia with pleuritic deposits over the right lower lobe and an adherent right diaphragm. The patient recovered from the bronchopneumonia and was discharged at the end of two weeks. Skin sensitization tests showed positive reactions to rye and cheese.

After a remission which lasted a few months the asthmatic attacks recurred, and until her admission to Mount Sinai Hospital on February 1, 1929, she was practically never free. She wandered about Europe and America without relief from any climate or medication. Five or six years ago edema of the ankles began and slowly spread upward involving the entire lower extremities. On admission there was a scarlet flush extending to the mid-thigh of two or three days' duration and attended by soreness and pain. There were also weeping ulcers of ten weeks' duration and tender. For seven months a progressive swelling of the abdomen had been noted. A few years previously there had been progressive diminution of the menstrual flow; three months later there was amenorrhea which persisted. The previous frequent cough with profuse white, tenacious expectoration had become considerably lessened.

Physical Examination.—She was acutely dyspneic and orthopneic. The chest expansion was considerably limited; marked supraclavicular retraction; the pulmonary resonance was increased. The breath sounds were vesicular, the expiration prolonged. There were a few high and low pitched musical râles. The voice and fremitus were unchanged on auscultation. The heart was much enlarged, especially to the right. There was a high pitched, musical murmur at the apex transmitted toward the sternum. At the base of the heart there was a systolic murmur which was short and localized to the second and third spaces to the right of the sternum. A gallop rhythm was at times noted. The rate was irregular, probably due to extrasystoles. The liver was palpable four fingers below the free border of the ribs. The spleen was not felt. Both lower extremities were reddish blue and swollen to twice the normal size by marked pitting edema. Several irregular, shallow ulcers on both legs were covered with a greyish slough. The edema extended up to the buttocks. There was no clubbing of the fingers. The hemoglobin was 102 per cent,

leucocytes 9,600, polymorphonuclears 80 per cent, eosinophiles 4 per cent, lympho cytes 10 per cent, monocytes 4 per cent. The blood urea was 18.0 mg., cholesterol 216 mg., glucose 107 mg. per 100 c.c. The urine varied in quantity between 400 and 600 c.c. a day, and revealed a trace of albumin the first day but none there-after. The pulse rate varied between 100 and 120; the temperature was normal. Roentgenograms showed "marked enlargement of the heart to the right and to the left, due to advanced mitral lesion." The lungs were much congested. There was a pneumonic process occupying the mesial portion of the right lower lobe. In the right lung there were a number of small shadows which are probably due to emphysematous areas in the lung.

The diagnosis was "asthma, emphysema, hypertension of the pulmonary circula-tion, myocardial insufficiency." She was treated with digitalis and salyrgan and a Karell diet, but without much improvement. On the fourth day after admission she was found by the nurse deeply cyonotic, gasping for breath and pulseless. She died ten minutes later.

Autopsy Protocol.—Body is that of a well-nourished, adult female, 34 years of age. There is marked cyanosis of the lips, face and fingers. The conjunctivae are markedly congested. The abdomen is distended. Both lower extremities are equally swollen to about twice the normal size, the swelling being most marked below the knees. There is pitting edema over the legs, and on the posterior aspect of the lower half of the legs are noted several irregular, shallow ulcers with a grayish-white base. There are no clubbing of the fingers, jaundice or petechiae. On open-ing the veins of the neck the blood gushes out as though under pressure, rising to about 3 inches above the level of the vein. It is noted that all the loose alveolar tissue of the body, especially that in the pelvis, shows marked degree of anasarca, the tissues being easily separated from the bony structures.

Chest: The pleural cavities contain a few centimeters of clear fluid. Both lungs weigh 1225 gm. The left upper lobe is bound down to the chest wall by fresh fibrous adhesions, easily torn through. The right lung is bound down more firmly, especially to the diaphragm and to the upper part of the chest wall. These latter adhesions can be broken through only with some difficulty, tearing the parietal pleura off the chest wall. Both lungs are markedly emphysematous, especially the right, which shows on its surface marked bulbous emphysema, the blebs reaching the size of a small plum. The left lung is elastic and crepitant. The cut surface of the upper lobe is dark red, fleshy and hemorrhagic, while the lower lobe reveals a well-aerated and normal appearing surface. The right lung was not opened. The trachea is negative. The bronchi, especially in their smaller branches, show an edematous and inflamed mucosa. There are numerous patches of dense fibrous lung; these patches are most conspicuous in the peripheral portion of both organs.

Heart: The right ventricle and auricle are tremendously dilated and somewhat hypertrophied, taking up the entire anterior aspect of the heart and overlapping the left auricle and ventricle. The left ventricle is normal in size. The heart weighs 525 gm. The myocardium is firm and dark red. The pulmonary orifice measures 8.75 cm. The valves are normal. The aortic orifice is 6.25 cm. in circum-ference. The wall of the pulmonary artery is thicker than normal, and in the finer branches are noted many small yellow areas of atherosclerosis. The aorta is elastic and, grossly, normal. The coronary arteries are patent. The pericardium is smooth and glistening, and the pericardial sac contains about 200 c.c. unclotted blood. In conjunction with this there is noted a small hemorrhagic spot on the anterior wall of the right ventricle which is apparently due to a puncture wound made by a needle. The tracheobronchial glands are enlarged but are grossly normal.

Abdomen: The peritoneal cavity is filled with about 800 c.c. golden-brown, clear fluid. The peritoneum is smooth and glistening. The intestines are con

gested. The iliac veins are prominent. The liver is smaller than usual, weighing 1425 gm. The capsule is opaque in spots. Cut section reveals the dark-brown mottled appearance of congestion. The portal vein is normal. The gall bladder and biliary tracts are normal. The kidneys are similar in appearance, showing fetal lobulations, and weighing 180 gm. each. The capsules, except where they dip in between the lobulations, strip easily, leaving a smooth dark red surface. Cut section reveals a dark red surface, a widened cortex with normal markings. The bladder is small. The pancreas and adrenals are normal. The spleen weighs 150 gm., is bluish-red and fairly firm. Cut section shows a deep red surface which is not diffluent; the pulp barely scrapes. The Malpighian bodies are rather indistinct.

Genitals: The ovaries are small and equal in size and show no gross disease. The uterus is small and multiparous in type. The venous sinuses in the uterine wall are dilated. The veins in the broad ligament are prominent. The vagina is normal.

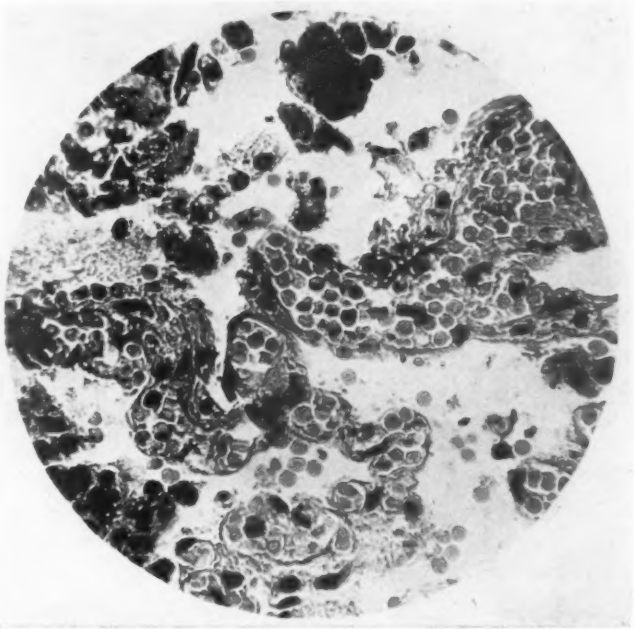

Fig. 7.—Arteriocapillary fibrosis of the lung secondary to asthmatic emphysema, showing extensive dilatation and thickening of the capillaries.

G. I. Tract: The esophagus is bluish-red. The stomach is filled with large amount of semi-fluid, tarry-colored material. The blood vessels are prominent. The entire small intestine shows a congested mucosa, more marked in the proximal portion. The large intestine is filled with a small amount of light yellow feces. The mucous membrane shows no congestion.

Bacteriological Examination: Lung tissue negative for monilia.

Microscopical Examination: The pancreas shows small areas of fibrosis and atrophy of periphery of lobules. The liver shows central congestion and hemorrhages, edema. The thymus shows retrogressive changes. The myocardium is normal. The ovary shows few follicular cysts. The spleen shows the Malpighian bodies prominent; the pulp appears hemorrhagic. The thyroid shows the acini are distended with colloid; the epithelium is flattened. The kidneys are markedly congested. The

lumen of the tubules is filled with cellular débris. Many red blood cells are present in the glomerular spaces.

Lungs: With the low power magnification the section reveals different areas of irregular density varying from a vesicular appearance to that of almost complete consolidation. With the high power magnification the walls of the alveoli in the vesicular areas appear enormously thickened, and the lining intimal endothelium is prominent (Fig. 7). In the consolidated areas the alveoli are very small and in many instances almost completely obliterated. The lining epithelium is high cylindrical and presents the glandular appearance of an embryonal lung. The contraction and obliteration of alveoli is due entirely to an enormous transformation of the alveolar septa into fibrous connective tissue; the capillaries are almost entirely obliterated in these septa (Fig. 8). In tracing the microscopic

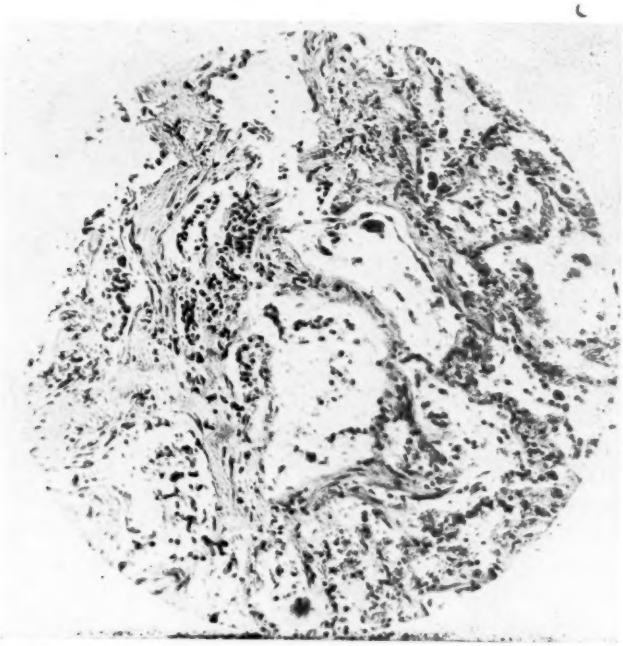

Fig. 8.—Advanced stage of arteriocapillary fibrosis of the lung consequent to asthmatic emphysema showing extensive fibrosis of the alveolar walls.

appearance of the septa from the vesicular to the denser consolidated areas one notes the increasing fibrosis, the capillaries becoming fewer in number until they are almost absent. Here and there one notes patches of apparent hyaline change in the walls of the alveoli. The pulmonary vessels are intensely arteriosclerotic: the arterioles, especially in and around the sclerotic portions of the lung, are almost entirely occluded by intimal proliferation, suggesting that part of the sclerosis of the alveolar walls might be the result of shutting off or diminution of the blood supply. The muscular tissue in the septa shows enormous hypertrophy. Most of the alveoli contain the characteristic pigmented "heart failure" cells.

About the bronchi there are extensive areas of fibrosis with lymphatic infiltration. The peribronchial, periarterial and septal lymphatics are filled with many lymphocytes. The bronchial epithelium in places is markedly flattened and in some places consists of a number of layers of squamous cells. The basement membrane is much thickened and has a hyaline appearance. There is hyperplasia of the mucous

glands of the larger bronchi. The bronchial musculature appears hypertrophied. Most of the bronchi contain what appears to be mucinous material. The pleura is thickened by fibrous tissue.

Diagnosis.—Chronic emphysema of both lungs; chronic bronchitis; arteriosclerosis and dilatation of pulmonary artery; dilatation and hypertrophy of the right auricle and ventricle; chronic passive congestion of liver, kidneys, spleen and intestines; ascites; anasarca.

Summary.—A woman acquires bronchial asthma at the age of 26 years. Under observation there is noted a transition from spasmodic asthma to continuous asthma, to emphysema, to the symptom-complex of pure hypertension of the pulmonary circulation, and finally to death from failure of the right side of the heart. At autopsy, dilatation and arteriosclerosis of the pulmonary vessels are found, with hypertrophy of the right ventricle, marked emphysema, patchy fibrosis of the lungs, and the conventional evidences of chronic congestion of the viscera. Microscopically, the lungs reveal profound dilatation of the capillaries and thickening of their walls with transition to obliteration of the capillaries and complete fibrosis of the alveolar septa, lesions, in other words, of an extensive arteriocapillary fibrosis or pneumonia of heart disease.

This is, therefore, an unusually sharp and unmixed case of hypertension of the pulmonary circuit, revealing the independence in incidence between the arteriosclerosis of the lesser circulation and that of the greater circulation, and showing the sequential relationship of arteriosclerosis to pressure changes. In the greater circulation the aorta was normal because the pressure was normal, and the patient did not live long enough for the normal pressure to cause arteriosclerosis (decrescent arteriosclerosis). It has been repeatedly observed that arteriosclerosis of the pulmonary vessels can occur at any age, even during infancy, provided a cardiac disorder is present that gives rise to a heightened circulatory resistance somewhere within the pulmonary circuit, for instance, an open interventricular septum. Decrescent arteriosclerosis is rare in the pulmonary arteries because the intravascular pressure is low, one-sixth that within the aorta, according to Starling.

The case also reveals in striking fashion the genesis of pneumonia of heart disease from a lesion that was primarily not within the heart at all, but from a resistance within the pulmonary capillary bed. Histologically, nevertheless, it differs in no way from the conventional pneumonia of heart disease arising, for instance, from a mitral stenosis.

CONCLUSIONS

1. Brown induration of the lung (Stauungs-induration) only occurs in the forms of circulatory or cardiac disturbance in which a hypertension of the pulmonary circulation can be predicated, no matter where the increased peripheral resistance may be.

2. The lesions are exclusively associated with arteriosclerosis of the pulmonary vessels. Arteriosclerosis of the pulmonary vessels is, there-

fore, pathognomonic of hypertension of the pulmonary circuit and vice versa.

3. The lesion of brown induration of the lung consists essentially in dilatation and thickening of the pulmonary capillaries. It is an "arteriosclerosis" in miniature. Unquestionably, part of the sclerotic process is the result of diminution in blood supply and even infarction of the affected areas.

4. The lesions within the lung parallel exactly those seen in the systemic organs, and especially in the kidney, in hypertension of the greater circulation.

5. A case is reported in which the lesions of the brown induration of the lung were found consequent to a prolonged asthma. Under observation, the patient revealed the transition from a purely functional bronchial asthma to emphysema, to a pure clinical example of hypertension of the pulmonary circulation and finally to death from failure of the right heart.

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AURICULAR FIBRILLATION AS THE ONLY MANIFESTATION OF HEART DISEASE*

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IT IS well recognized that auricular fibrillation is ordinarily associated with evident structural change in the heart. This irregularity may, however, be the only manifestation of heart disease, and probably occurs under these circumstances more frequently than is generally appreciated. The present report of ten cases is intended to emphasize this fact.

The following are brief records of our cases:

Case 1.—D. S., a male medical student, aged 24 years, was admitted to the University Hospital January 8, 1928. He stated that while another student was removing cerumen from his ear with a metal instrument he suddenly felt nauseated and weak, and fainted. He was unconscious about thirty seconds. His fellow students observed a short period of cardiac standstill and then the beginning of the absolute irregularity. When he was examined by one of us thirty minutes later, there was auricular fibrillation, and he complained of palpitation and weakness. The patient walked to the hospital the following morning and the auricles were still fibrillating. Sinus rhythm returned spontaneously after twenty-four hours. On discharge the heart was normal in all respects.

Case 2^{22}.—R. H., aged 27 years, a hospital interne, whose heart had always been perfectly normal, suddenly found himself with auricular fibrillation (checked electrocardiographically) after a swim in an indoor pool. The event occurred in midwinter, at a time when the patient had had no such strenuous exercise for months. The arrhythmia disappeared spontaneously after twenty-four hours. Careful and complete examination at this time showed no evidence of heart disease.

Case 3.—H. R., male, aged 22 years, was admitted to the University Hospital, March 11, 1930. He complained of paroxysms of rapid heart action which had appeared at irregular intervals for five years. These attacks were induced by excitement, exertion, or alcohol; and in some instances there was no apparent cause. The duration varied from a few minutes to twenty-four hours. The referring physician had observed attacks of auricular fibrillation with a cardiac rate of from 160 to 170 per minute which persisted from six to ten hours. The first examination at the hospital revealed auricular fibrillation. Sinus rhythm was resumed spontaneously, and an attempt to reproduce the auricular fibrillation by exercise resulted in a paroxysm of auricular tachycardia during which the patient experienced an entirely new sensation. Later four ounces of medicinal whisky failed to induce auricular fibrillation. On discharge the heart was entirely normal. Small doses of quinidine sufficed to prevent recurrences.

Case 4.—V. S., a star football player, aged 20 years, was seen March 7, 1929, because of palpitation of the heart. Following a period of intoxication by bootleg alcohol he was conscious of the sudden onset of a rapid irregular heart action

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which persisted for several hours and was associated with a cramp-like sensation in the chest. He had a recurrence of these cardiac manifestations a few days later following another drinking bout. When examined subsequent to the last attack the heart was normal.

CASE 5.—T. R. M., a male, aged 32 years, was admitted to the University Hospital July 30, 1928, because of mild diabetes mellitus. At the age of eighteen years he was in bed for two days with painful joints, but there was no evidence of cardiac involvement at that time. Examination revealed auricular fibrillation which was verified by the electrocardiogram. The patient stated that the irregularity had been present for about three years and was first noticed one morning following a night of extreme intoxication from alcohol of questionable purity. The normal mechanism was restored by the administration of quinidine after which the heart was entirely normal. There was no recurrence of the irregularity. The patient later died following an operation for carcinoma of the rectum, and at necropsy the heart was found to be normal.

CASE 6.—An electrician, aged 25 years, reported to the University Hospital August, 1928, while intoxicated. He complained of a peculiar sensation in the precordium which had been present for about one hour. Upon examination there was a very rapid, irregular heart action with a marked pulse deficit. He denied previous cardiac symptoms, and there was no history of rheumatic or venereal infection. The auricular fibrillation disappeared during the night and did not recur.

CASE 7.—F. S., an Italian male, aged 34 years, was admitted to the University Hospital January 6, 1930. He complained of a queer sensation in the epigastrium which extended over the precordium. He had noticed a rapid heart action with exertion and excitement, but there had been no shortness of breath. The symptoms were first noticed two weeks prior to admission while working in a refrigerator car in which he detected gas. Upon examination auricular fibrillation was obvious and was verified by the electrocardiogram. The normal cardiac mechanism was restored by quinidine after which the heart was normal.

CASE 8.—E. M., male, aged 17 years, was admitted to the University Hospital because of deformities following infantile paralysis. He denied rheumatic fever and venereal infection. When seen prior to an operation on the leg, the heart was normal. Nitrous oxide and ether anesthesia were employd. On the evening after the operation and the following morning auricular fibrillation was noted. Sinus rhythm was resumed spontaneously after twenty-four hours and persisted.

CASE 9.—F. P., a male student, aged 28 years, was examined at the University Hospital April 30, 1929. He was employed in an oil station after school hours. He had always been active, and his past history was unimportant. Two days prior to the examination he noticed a short period of cardiac irregularity while studying. On the morning of the examination the cardiac symptoms recurred on arising, and shortness of breath was experienced. When he was examined in the afternoon, the findings were those of auricular fibrillation. After eleven hours of relative rest the normal rhythm was restored. The heart was then normal. The patient discontinued his work in the oil station, and there has been no further recurrence of the irregularity.

CASE 10.—J. D., male, aged 24 years, was admitted to the University Hospital May 12, 1930. He also was employed in an oil station. About six months prior to admission he noticed the sudden onset of a rapid heart action which lasted for only a few minutes. Three weeks later there was a return of the cardiac disturbance which persisted. When he was examined, the clinical and electrocardiographic manifestations were those of auricular fibrillation. Sinus rhythm was established by the administration of quinidine. Later there was a short paroxysm

of nodal tachycardia, but there has been no further interruption of the normal mechanism. At the time of discharge from the hospital there were no clinical or laboratory evidences of cardiovascular or thyroid disease.

In thirty-five cases collected from the literature, in which auricular fibrillation was the only manifestation of cardiac damage, the irregularity was attributed to a variety of stimuli, including electric shock, intraabdominal diseases, emotion and effort, and to intoxication by many different chemical substances.

In the collected cases and in those of our own series, the factors usually responsible for auricular fibrillation, such as arteriosclerosis, Graves' disease, rheumatic heart disease, and acute infectious diseases, were excluded. It is thus evident that paroxysmal or even permanent auricular fibrillation may be induced in apparently normal hearts. In four of the reported cases the irregularity was permanent. These occurred before the advent of quinidine medication. In a case reported by Reid[9] normal rhythm was restored by quinidine after two and two-thirds years, and in one observed by Hay and Jones[2] after five weeks. In one of our patients sinus rhythm was restored by quinidine after two and one-half years of auricular fibrillation. It is to be recalled that this heart (Case 5) was later found to be normal at necropsy. In two other cases in our series auricular fibrillation yielded to quinidine, one after five months and the other after two weeks. The auricular fibrillation in these five cases would probably have persisted also had quinidine not been given.

In four of the thirty-five collected cases the abnormal cardiac mechanism followed electric shocks which varied from 220 to 15,000 volts. This exciting factor is comparable to the faradic current used to produce auricular fibrillation experimentally in animals. The irregularity in those cases lasted from one day to five weeks, and in the latter sinus rhythm was restored by quinidine.

It is interesting to note that intraabdominal disease was held responsible for the auricular fibrillation in eight of the thirty-five cases. Felberbaum and Finesilver[6] reported a series of five cases, in three of which the cardiac irregularity occurred during or following attacks of gall bladder colic. In one there were four, and in another five paroxysms of auricular fibrillation, and the paroxysms appeared only with attacks of colic. Another patient in this series experienced the cardiac irregularity only during the distress of peptic ulcer. Cowan[5] recorded two instances of auricular fibrillation, one of which was associated with a gastrointestinal upset following purgation, and the other followed an indiscretion in diet. Wolferth[7] observed a paroxysm of auricular fibrillation during an attack of acute appendicitis.

The relationship between abdominal symptoms and cardiac irregularities has been recognized for many years. Austin Flint[23] made the following statement in 1885: "Paroxysms of disordered action of the

TABLE I

CASE	AGE	ETIOLOGY	LONGEST DURATION	RECURRENCE	E.K.G.	REMARKS	REPORTED BY
1	35	Electric shock	1 day	0	Polygraph	Might have been flutter	Laslett[1]
2	35	Electric shock 250 volts	5 weeks	2 attacks	Yes	Remained regular after quinidine	Hay and Jones[2]
3	31	Electric shock 220 volts	1 day	0	Yes		Wartenhorst and Rihl[3]
4	37	Electric shock 15,000 volts		Repeated	Yes	Better than average endurance before accident	Dick[4]
5	53	Exertion and gastric upset	1 day	2 attacks	0	No evident heart damage	Cowan[5]
6	58	Over-eating	Short	Repeated	0	Associated with indiscretion in diet	Cowan[5]
7	65	Gall bladder colic	10 hours	5 attacks		Only with gall bladder colic	Felberbaum and Finesilver[6]
8	54	Gall bladder colic	10 days	4 attacks	Yes	Only with gall bladder colic	Felberbaum and Finesilver[6]
9	34	Gall bladder colic	24 hours	0	0		Felberbaum and Finesilver[6]
10	52	Peptic ulcer distress	24 hours	Repeated	Yes	Only with gastric distress	Felberbaum and Finesilver[6]
11	36	Acute abdominal distress	Short	Repeated	Yes	Extensive postoperative adhesions	Felberbaum and Finesilver[6]
12		Acute appendicitis		0	0		Wolferth[7]
13	23	Cough	Short	Became permanent	Polygraph	Necropsy showed normal heart	Gossage and Braxton Hicks[8]
14		Sudden exertion	10 years	Persisted	Polygraph	Struggled with horse	Hay and Jones[2]
15	50	Sudden exertion	Short	2 attacks	Yes	Heart normal the previous day	Hay and Jones[2]
16	32	Exertion	2⅔ years	0	Yes	Stopped with quinidine. Heart normal	Reid[9]
17	32	Sudden effort and fright	14 years	Persisted	0	Frightened and climbed over high wall	Hay and Jones[2]
18	24	Nervous shock from explosion	Short	Repeated	Yes	Very nervous	Semerau[10]
19	22	Nervous tension. Surgeon	5 days	4 attacks	Yes	1. Paratyphoid. 2 & 4. During long operation. 3. Exertion	Hamburger[11]
20	32	Epinephrine and exertion	2 hours	0	Yes	Very nervous	Smith and Moody[12]
21	39	Epinephrine and deep breathing	Short	Repeated	Yes		Smith and Moody[12]

TABLE I—CONT'D

CASE	AGE	ETIOLOGY	LONGEST DURATION	RECURRENCE	E.K.G.	REMARKS	REPORTED BY
22	27	Alcohol	36 hours	0	0	Normal heart	Patterson[13]
23		Alcohol		0	0		Wolferth[7]
24	30	Alcohol, smoking and over-eating	Few hours	0	0	Normal heart	Patterson[13]
25	52	Arsenic 6 gr.	24 hours	0	0	Associated gastrointestinal upset	Cassidy. Quoted by Cowan[5]
26	42	Salvarsan		0	Yes	Gangrene of lung. Chill and collapse after salvarsan	Semerau[10]
27	44	Hydrogen sulphid	Few hours	0	Yes		Robinson[14]
28	50	Aspirin gr. 20	3 days	0	0	Normal heart before	Gupta[15]
29	42	Ether anesthesia	Short	Repeated	Polygraph	Remained normal	Fox[16]
30	47	Digitalis	Short	0	Polygraph	Had paroxysmal tachycardia. A.F. began with digitalis	Mackenzie[17]
31	35	Diabetic coma	Short	Repeated		Later developed myocardial insufficiency	Borg[18]
32	43	Injury to left chest		Persisted		Normal heart prior to accident	Bullrich and Lacroze[19]
33	29	Kyphoscoliosis	2 days	Repeated	Yes		Boas[20]
34			Short	Repeated	0	Athletic young male	Levine[21]
35			Short	Repeated	0	Athletic young male	Levine[21]
36	24	Instrumentation of ear	24 hours	0	0	Syncopal attack followed by fibrillation	This report
37	27	Exertion	24 hours	0	Yes	Disappeared spontaneously	This report
38	22	Exertion, excitement, alcohol	10 hours	Repeated	Yes	Also nodal paroxysmal tachycardia	This report
39	20	Alcohol	Short	Repeated	0	Two attacks after drinking	This report
40	32	Alcohol	2½ years	0	Yes	Stopped with quinidine. Heart normal at necropsy	This report
41	25	Alcohol	Short	0	0		This report
42	34	Gas in refrigerator car	2 weeks	0	Yes	Stopped after quinidine	This report
43	17	Anesthesia	Short	0	0	Heart normal before and after attack	This report
44	28	Oil station	11 hours	2 attacks	0	No recurrence since change in occupation	This report
45	24	Oil station	2 months	Repeated	Yes	No recurrence since change in occupation	This report

heart are often accompanied by gastric flatulence, and gaseous eructations afford relief." Hoover[24] has contributed the most comprehensive discussion of the subject in the last edition of Osler's *Modern Medicine* (1927). He cites a case in which functional heart-block resulted from gaseous distention of a stomach diffusely involved by carcinoma: "Such symptoms must certainly have been caused by excitation near the cardia and not from upward displacement of the diaphragm." In a second case, premature beats were induced whenever there was as much as a pint of water in the stomach. This he attributed to a low threshold for the vagus reflex. Finally he reported the following case: "A man who for years has suffered from stomach symptoms (that have never been satisfactorily explained) on several occasions developed auricular fibrillation. During the attacks neither ventricle was enlarged but the right auricle was enlarged to the right of the sternum. These attacks accompanied functional disturbances in the stomach motility and ceased without medication just as suddenly as they began. Thus far the heart has shown no evidences of disease and although for several years these attacks of auricular fibrillation have recurred at irregular intervals, the heart has apparently lost none of its reserve energy."

The mode of production of auricular fibrillation in disease of the abdominal viscera is of special interest. In all of the reported cases the offending lesion was in a viscus supplied by the vagus nerve. It would seem that a reflex stimulation of the heart through the vagus was probably the exciting factor. This feature is best illustrated by the first case in our series in which stimulation of the sensory endings of the vagus in the external auditory canal produced cardiac syncope which was followed by auricular fibrillation. Other factors such as pain, fright, exertion, infection and intoxication were not present.

Excitement, exertion and high nervous tension appeared to be factors in cases reported by Hay and Jones,[2] Smith and Moody,[12] Semerau,[10] Hamburger,[11] and by Reid.[9] Hay and Jones reported a case of auricular fibrillation in a patient who was frightened by a dog and climbed over a high wall, and another in a man who struggled with a horse. In both instances the irregularity persisted. A nervous element seemed to be the outstanding feature in the patients studied by Smith and Moody. In one, excitement regularly induced a rapid irregular heart action, and attacks were also precipitated by the administration of epinephrine and by deep breathing. The second case was very similar. In the patient studied by Semerau the disordered cardiac mechanism was induced by the nervous shock of an explosion. Hamburger's patient, who was a surgeon, experienced his first paroxysm of auricular fibrillation during the course of paratyphoid fever. His second and fourth attacks occurred during long operations which were attended by high nervous tension, and the third attack

was attributed to exertion. In one of our cases auricular fibrillation followed swimming which was unassociated with emotion.

The importance of impure alcohol in the production of auricular fibrillation deserves special mention. In four of our patients and in three of the collected cases the onset of the irregularity followed a drinking bout. In our cases the alcohol was of questionable purity, and the others occurred in the United States since the advent of the Eighteenth Amendment. One of our patients who stated he always experienced rapid irregular heart action after drinking alcohol was not affected by four ounces of medicinal whisky. It would seem that the irregularity might be attributed to some impurity in the alcohol.

In three of our cases there was a possibility of carbon monoxide inhalation. Conduction defects have been reported by Colvin[25] and by Haggard[26] in very severe grades of carbon monoxide poisoning. None of our patients inhaled enough of the gas to produce symptoms and certainly not enough to produce the anoxemia which is assumed to be the cause of the conduction defects. The gas which the patient in Case 7 encountered in the refrigerator car was no doubt from the charcoal burner with which such cars are heated during the winter. The possibility of carbon monoxide poisoning under such circumstances is well recognized by railroad authorities. The other two patients were attendants at gasoline stations, one of whom was exposed to fumes in a closed garage. These patients were very careful in the handling of ethyl gasoline but both inhaled some volitalized gasoline of all grades.

In ten of the collected cases and one of our own, auricular fibrillation was attributed to such agents as arsenic, salvarsan, hydrogen sulphide, aspirin, ether anesthesia, digitalis, diabetic coma, injury to the chest, spinal deformity and cough. In the case in which arsenic was mentioned as the probable precipitating factor there was an associated gastrointestinal disturbance which may have been important in the production of the auricular fibrillation. There is also a possibility of vagal stimulation in the case in which the irregularity was precipitated by coughing. Finally, Levine[21] recorded two healthy young adults with paroxysmal auricular fibrillation for which he gave no etiological factor.

The various exciting causes appear to be unrelated. The induction of the auricular fibrillation under these circumstances is possibly dependent upon some common basic disturbance in the auricles. It is not possible to exclude minor degrees of cardiac damage as being fundamentally responsible for the altered rhythm. If we grant an anatomical basis, the damage is no doubt of minor importance compared to that ordinarily encountered and probably is confined for the most part to the auricles. It may be a temporary lesion or a disturbance of function alone. In some instances the lesion may subsequently pro-

gress to the point where structural changes can be detected by the present methods of examination. The future course of these patients may decide this question.

SUMMARY

Ten patients are reported in whom auricular fibrillation was the only evidence of cardiac disease. The factors usually responsible for this irregularity were excluded. The age ranged from seventeen to thirty-four years, and all except two were under thirty years of age.

In seven cases the auricular fibrillation was paroxysmal, while in three it had persisted for periods of two weeks, five months, and two and one-half years respectively. In each of the latter instances sinus rhythm was restored by quinidine. The auricular fibrillation in these three cases would probably have continued had quinidine not been given. The patient who had auricular fibrillation for two and one-half years later came to necropsy, and the heart was regarded as grossly and microscopically normal.

In one of our cases the auricular fibrillation was attributed to the removal of cerumen from the external auditory canal, one to exertion, four to alcohol, one to carbon monoxide, one to ether and nitrous oxide anesthesia and two were in attendance at gasoline stations.

In the thirty-five cases collected from the literature the auricular fibrillation was attributed to such stimuli as electric shock, diseases within the abdomen, emotion and effort and intoxication by various chemical substances.

Abdominal disease and alcohol were the most common exciting agents. In the former group it is believed that a reflex stimulation over the vagus contributed to the production of auricular fibrillation.

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THE CHANGES IN CIRCULATION FOLLOWING BIRTH*

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THE results of several recent investigations indicate that certain long cherished traditions as to the fetal circulation must be relinquished. That this new information has come fragmentarily from various independent workers and is still mutually confirmatory gives it especial weight. Since interpretation of the changes in circulation which follow birth must start from fetal conditions as a basis, it seems pertinent to reexamine both these closely related subjects in the light of our present information.

Controversies concerning the course of blood through the fetal heart have been smouldering, with periodic outbreaks, ever since the times of Harvey. The historical phases of the subject have been thoroughly covered by Pohlman[9] (1909) and more recently by Kellogg[3] (1928). The striking thing is the persistence of the Sabatier[11] (1791) doctrine that the entire inferior caval stream carrying the freshly returned placental blood passes directly through the foramen ovale to the left atrium, while the superior caval current of blood, depleted by a systemic circuit, passes with little or no mingling into the right ventricle. Possibly there exists, because of greater familiarity with the adult circulation where separation of pulmonary from systemic blood is so strikingly maintained, an unconscious bias toward interpreting the fetal circulation in terms of blood currents which maintain their identity. Whatever the underlying reasons may be, current textbook illustrations bear eloquent testimony as to the tenacity of the Sabatier conception in the face of an increasing accumulation of evidence against it.

Early injection experiments (e.g., Reid,[10] 1835) appeared to give some support to the Sabatier theory. But these experiments made with heavy starch masses in dead material, when reviewed in the original, appear too equivocal to justify the wide citation they have received.

Pohlman[9] (1909) carried out the first really critical experiments devised to ascertain the course of blood through the fetal mammalian heart. In living pig embryos he injected colored starch grains into the circulation and, by repeated counts of the grains appearing in blood recovered from the right and left heart, demonstrated that mixing of inferior and superior caval blood occurred in the right atrium. Clear cut as were Pohlman's results, they had little apparent influence on the propagation of the Sabatier theory of crossed pure currents.

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In 1928 Kellogg[3] repeated and extended Pohlman's experiments. Working with cats and dogs as well as pigs, and varying both the sites of injection and of recovery, Kellogg amply confirmed Pohlman's conclusions. Moreover, in a later paper (1929) Kellogg[4] has reported oxygen determinations made on blood recovered from both cavae and from both sides of the fetal heart which clearly indicate that the left atrium does not receive, by way of the foramen ovale, unmixed inferior caval blood freshly returned from the placenta.

Indication that the results of these experiments on animals are applicable to the human fetus is given by the work of Patten, Sommerfield, and Paff[7] (1929) on the functional capacity of the foramen ovale. Their study of the interatrial opening in the human fetal heart showed

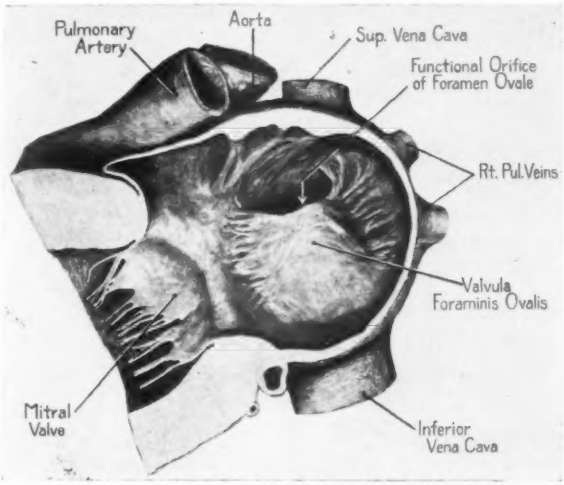

Fig. 1.—Interior of the left atrium of the human heart at birth (x 1½); based on a photograph of a scale model retouched from direct study of a group of normal specimens. The valvula foraminis ovalis is shown in the position assumed when a stream of fluid is forced through the inferior vena cava.

that the apparent capacity of the septal orifice is greatly reduced by the manner in which the valvula foraminis ovalis is attached to the septum. The measurements showed an effective interatrial communication less than 43 per cent of the cross-sectional area of the inferior caval inlet (Figs. 1 and 2). Even making the forced assumption of a rate of caval inflow sufficiently strong to form a definite current directed at the foramen ovale, this current could not pass through a crooked passage less than half the size of the caval inlet. Eddying back of more than half the inferior caval stream would inevitably result in the same sort of mixing of placental and systemic blood in the right atrium of the human fetus that Pohlman and Kellogg have demonstrated experimentally in other mammals.

The restricted functional orifice of the foramen ovale is of significance for other conditions than the mixing of blood currents in the right atrium. By reason of its small size the foramen ovale alone cannot pass on to the left side of the heart nearly enough blood to equalize intake on the left with intake on the right. In view of the fairly equal development of the two sides of the fetal heart any assumption that they do not handle approximately equal amounts of blood is untenable. The obviously neglected factor in this situation is the pulmonary circulation.

It is commonly stated that before birth there is very little blood passing through the pulmonary circuit. There seems to be no evidence of any sort adduced in support of this dictum. As far as one can trace its origin it is entirely the outgrowth of a theory as to the mechanism by which a radical rerouting of blood through the fetal heart is supposed to be brought about at the instant of birth. It has the unmistakable odor of teleology to postulate a capacious but virtually unused vascular plexus developing in the growing lungs, ready at the instant of birth to receive a suddenly rerouted current of blood carried to the lungs for oxygenation. While there are not as yet available any quantitative determinations of the blood flow through the fetal lungs, all the implications are against the current view that the pulmonary circulation is negligible. It is out of line with everything known about the development of the vascular system to think of vessels growing beyond a capacity consonant with their present activities. Nor is this argument by analogy the only angle of approach open. Injection or perfusion of the vascular tree of uninflated lungs seems to offer little if any more resistance than injection of inflated lungs. Moreover, measurements of the pulmonary vessels in individuals just before birth show them to be of virtually the same capacity as they appear in other individuals that died after breathing for two or three days.* The actual size of the fetal pulmonary veins as determined by these measurements indicates that they bring into the left atrium a volume of blood somewhat greater than that contributed by way of the restricted functional orifice of the foramen ovale. The fact that the left side of the heart receives much less blood by way of the foramen ovale than hitherto believed, but receives a correspondingly greater amount from the pulmonary circuit, leaves undisturbed our conception of an approximate right-left balance of cardiac load during fetal life. It does, however, radically lessen if indeed it does not eliminate entirely, the abrupt increase in pulmonary circulation which it was necessary, on the old basis, to postulate at the moment of birth.

*These figures for the pulmonary vessels and those that follow for other cardiac orifices are given from preliminary tabulations of work still in progress (Patten and Toulmin[8]). None of the average measurements here given are based on fewer than forty hearts. In some instances more than 100 cases have already been measured. The close agreement of sample group averages indicates that the results of the greater number of individual measurements it is planned to make before publication of the detailed data will differ but fractionally from those given here.

Most significant from the standpoint of postnatal changes are the additional facts that the pulmonary arteries are about the size of the umbilical arteries and the total cross-sectional area of the pulmonary veins about the same as that of the umbilical vein. The placental circuit adequately takes care not only of oxygenation, but also of food intake and waste elimination. If, therefore, the pulmonary vessels are carrying a circulation in any way consonant with their size there is enough blood already going to the lungs before birth to care for oxygenation as soon as the lungs are ventilated.

Fig. 2 summarizes graphically the points discussed above and indicates the revisions in the current interpretation of the fetal circulation

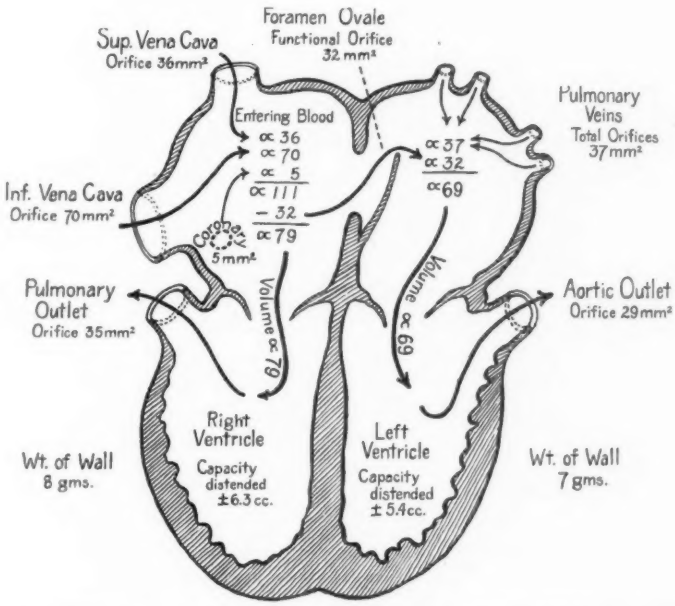

Fig. 2.—Schematic diagram showing dimensions of 20 gram heart from normal full-term fetus. For the sake of simplicity the measurements for this typical heart are given to the nearest integer. Tabulated measurements from a series of over fifty hearts ranging from 15 to 30 grams show the constancy of the significant relationships here indicated. (Patten and Toulmin.[8])

that they entail. There is mixing of the blood in the right atrium instead of crossed "pure currents." The restricted functional orifice of the foramen ovale brings, instead of practically all, less than half the blood entering the left atrium. On the basis of vessel size, the fetal pulmonary circuit brings in more than half the blood entering the left atrium. The blood shunted from right to left through the foramen ovale does not quite raise the blood volume estimated as entering the left atrium to equality with that entering the right. That this is a real difference and that the load carried by the right and left sides of the heart is not absolutely balanced is confirmed by the slightly

greater size of the right ventricular lumen, the slightly greater weight of the right ventricular musculature and the somewhat greater size of the pulmonary than the aortic outlet. These facts all accord with the characteristic right ventricular preponderance exhibited by electrocardiograms of the neonatal heart.

It is unwise to draw too specific conclusions about the circulation from such measurements alone. At present, however, there are available practically no pressure or volume determinations on the fetal circulation. In the sizes of the channels we have at least the start of a quantitative basis of interpretation hitherto lacking. That these measurements are not without functional significance is indicated by some simple comparisons.

In the fetus, aortic and pulmonary pressures may be assumed to be equal because of the free communication of these vessels through the ductus arteriosus. This assumption is in accord with the only experimental evidence we have on blood pressures in the fetal heart, Pohlman's observations that blood rises to equal heights in capillary tubes inserted in the right and in the left ventricles. If the pressures are equal, the relative size of the arterial outlets and the relative weights of the ventricular walls should both be indicative of the amount of blood handled by the right and left sides of the heart. In that case we should expect the two ratios to equal each other. That is:

$$\frac{\text{Right Ventricular Weight}}{\text{Left Ventricular Weight}} \text{ should equal } \frac{\text{Area Pulmonary Outlet}}{\text{Area Aortic Outlet}}$$

Writing into this proportion the actual measurements made on fetal hearts:

$$\frac{8}{7} \text{ should equal } \frac{35}{29}$$

The correlation figures at 0.94+ where 1 is the expectation.

Since the atria of the fetal heart are in open communication, some of the greater intake of the right atrium will tend to be passed on by way of the foramen ovale to the left atrium. If the blood entering the atria is proportional to the size of their vascular inlets, as is probable with the very low pressure there existing, we can indicate conditions empirically thus:

Entering Right Atrium			*Entering Left Atrium*	
Orifice of superior vena cava	36 sq. mm.			
Orifice of inferior vena cava	70 sq. mm.			
Orifice of coronary sinus	5 sq. mm.	Total cross-sectional area of pulmonary veins		37 sq. mm.
Total	111			
	−32 ⟶	Functional Orifice Foramen Ovale	⟶	32 sq. mm.
Blood volume	∝ 79 sq. mm.	inlets		∝ 69 sq. mm. inlets
	↓			↓
	Entering right ventricle			Entering left ventricle

If these figures are functionally significant, the ratio of blood received by the two ventricles should equal both the ratio of right to left ventricular weight and the ratio of pulmonary to aortic outlet. Substituting the figures obtained from actual heart measurements:

$\frac{79}{69}$ should equal $\frac{8}{7}$: Correlation computes at 0.98

And:

$\frac{79}{69}$ should equal $\frac{35}{29}$. Correlation computes at 0.94

These methods of comparison are, of course, crude from the mathematical standpoint and quantitatively the results should be regarded as tentative. When pressure measurements and flow determination can be added to the available evidence, more critical mathematical methods must be applied to the problem. Pending this time the existence of a roughly 8-to-7 relation between (1) right and left ventricular intakes as estimated empirically from the measurements of vascular orifices, (2) right and left ventricular weights, (3) right and left ventricular capacities and (4) pulmonary and aortic outlets, may be regarded as indicative of the nature of the right-left functional balance in the fetal heart.

Because the Sabatier idea of crossed blood currents in the right atrium has been so long entrenched, the conception that there is mixing of the blood in the right atrium is likely to meet with more resistance than either the idea of a prenatal pulmonary circuit of considerable volume, or the conception of the right-sided preponderance of the fetal heart. Such mixing of the blood may seem inefficient compared with condition in the adult, but this is a one-sided comparison. The fetus is an organism in transition. Starting with a simple ancestral plan of structure and living an aquatic life, it attains its full heritage but slowly. It must be viewed as much in the light of the primitive conditions from which it is emerging as in comparison with the definitive conditions toward which it is progressing. Below the bird-mammal level, circulatory mechanisms with partially divided and undivided hearts and correspondingly unseparated blood streams meet all the needs of metabolism and growth. Maintenance of food, oxygen, and waste products at an average level which successfully supports life does not depend on "pure currents," although such separated currents undoubtedly make for higher efficiency in the rate of interchange of materials. From a comparative viewpoint, the fact that the mammalian fetus is supported by a mixed systemic circulation seems but natural. Moreover, if the fundamental competence of such a circulation is emphasized rather than the respects in which it falls short of the perfected adult mechanism, we are not forced to postulate a series of abrupt and profound changes in the circulation at the time of birth,

nor are we continually puzzled by the "seemingly impossible size" of septal defects such as are not infrequently carried without serious handicap into maturity and even old age.

The changes occurring in the circulation postnatally must be re-evaluated in the light of this altered conception of the fetal circulation. According to the conventional interpretation, tying the cord reduces the volume of blood flowing from the inferior vena cava into the right atrium and thence through the foramen ovale to the left atrium. With the first breath, the preformed, but hitherto practically unused, pulmonary vessels suddenly open and allow a rush of blood to pass into the lungs. By the very power of its surge into the left atrium the blood returning from the lungs forces the valvula foraminis ovalis to close against the weakened caval current impinging on its right atrial face. Within a day or two, or perhaps a week, the valvula fuses to the septum and seals the foramen ovale. Inflation of the lungs shifts visceral relations, putting the ductus arteriosus on so much of a stretch that blood can no longer pass freely through it and, presto! the newborn infant has an adult type of circulation. It is a dramatic story lending itself well to diagrammatic exposition within brief compass, but it will not stand scrutiny.

In its older form, the idea of the immediate closure of the foramen ovale was crudely mechanical. There was supposed to be an active shutting off of this passage which forced a rerouting of the blood through the heart. If such closure failed to occur, cyanosis and death were supposed to result. One will find this view still expressed in many current textbooks of embryology and obstetrics. And case after case can be found in present-day hospital and public health records implying the same viewpoint by accusing an open foramen ovale of being the cause of death in a neonatal individual where an open foramen ovale is absolutely normal. Belated recognition of the long-known fact that closure of the foramen ovale is not completed until several months after birth is slowly forcing a retreat from such traditions. The present view is essentially that although anatomical closure of the foramen ovale is delayed, its functional closure is immediate.

Even this modified conception of an immediate closure which is functional rather than anatomical is a corollary of the old Sabatier hypothesis. The first critical event leading toward closure is supposed to be a reduced inferior caval current due to interruption of the placental circuit. If, as recent work clearly indicates, there exists no pure current of inferior caval blood traversing the right atrium and making its way directly through the foramen ovale, this contention loses all weight. If there is free mingling of the blood currents entering the right atrium, flow through the foramen ovale must be determined by the difference between the rate of intake and the resultant pressures which exist on either side of the interatrial septum. Unfor-

tunately we have no experimental data on these critical matters. But what effective reduction can interruption of the placental circuit bring about in the relative volume or pressure of blood entering the right atrium as compared with that entering the left? No maternal blood was coming to the fetus from the placenta. After the tying of the cord, as before, all the blood in the systemic circuit must return to the right atrium. Possibly after the placenta is cut off, relatively more blood enters through the superior cava. But change in the relative amount of blood returned by the two cavae will not alter the pressure relation between right and left atria. As far as the heart is concerned the immediate result of tying off the umbilical vessels is merely to eliminate from the fetal circulation the blood that happened to be passing through the placenta at the moment. It can have no more effect on relative pressures in the two atria than loss of the same amount of blood by superficial hemorrhage. One might as well try to effect the closure of the valvula foraminis ovalis by carrying out simultaneously hyperdermoclysis in the drainage area of the superior cava and venesection in the territory drained by the inferior cava.

As to the ductus arteriosus being abruptly occluded by traction on it incident to the first inspiration, a little dissection and some experimental pulling and hauling on that tough-walled vessel will make one exceedingly skeptical. Furthermore in case after case of congenital aortic stenosis the ductus arteriosus remains open, pouring a supplementary stream into the deficient aortic current. Conversely in cases of true congenital pulmonary stenosis the ductus quite commonly remains open with blood from the aorta going through it to the lungs in reverse of the normal direction of fetal flow. If in such experiments, obligingly performed for us by nature, complete inflation of the lungs fails, over a period of months or even years, to effect the closure of a ductus arteriosus which is carrying merely a supplementary blood current from a more or less crippled heart, how can we look to such a mechanism to close off abruptly at the moment of birth, a blood stream equal in power and volume to that of the isthmic part of the fetal aortic arch? (Fig. 3.)

The idea that the pulmonary flow is negligible before birth and rises abruptly to full power with the beginning of respiration is, as far as a diligent search of the literature reveals, pure dogma. As was stated above, no direct observations have been made on the volume of the pulmonary flow before birth, but the circumstantial evidence, first of the size of the vessels and second of the right-left unbalance that would exist in the fetal circulation if these vessels were not operating at capacity, strongly indicates that the pulmonary circuit before birth is a dynamic factor which cannot be ignored. But, although the pulmonary vessels are equivalent in size to the umbilical vessels, the total

cross-sectional area of the pulmonary veins at the time of birth is approximately only one-third of the total cross-sectional area of the veins entering the right atrium. (Fig. 2.) It entails an incredible series of assumptions to juggle pressures and rate of flow in such a manner as instantaneously to balance the output of one group of veins against the output of another group having three times their bore. Yet this is demanded by the theory that an immediate closure of the valvula foraminis ovalis is brought about by prompt equalization of left and right atrial pressures.

The existence of doubt concerning, or positive evidence against, each separate event in the chain of happenings invoked to throw the switches for an immediate and radical rerouting of blood at the time of birth should give us pause. Is not the very existence of such abrupt changes as unsupported as the elaborate series of occurrences supposed to explain them? Let us look without preconceived prejudice

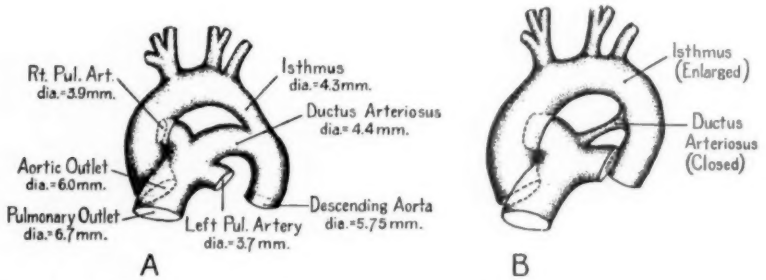

Fig. 3.—Diagrams showing the characteristic postnatal change in the isthmic region of the aortic arch. *A*. Fetal condition at full term. The vessel diameters are averages from the measurements of thirty cases. *B*, Typical configuration three to four months after birth. Note the enlargement of the isthmic portion of the aortic arch which accompanies the reduction of the ductus arteriosus.

at the possibility that the changes in the circulation following birth are accomplished gradually and without abrupt rerouting of major blood currents.

The fact that, even though it is much greater in volume than has hitherto been recognized, the pulmonary circuit at birth is still relatively considerably smaller than it is in an adult, does not seem to offer any great difficulty. In the first place it is of the same order of magnitude as the placental circuit which has been caring for not only gaseous interchange but also food intake and waste elimination. In the second place the high red cell count and the high hemoglobin index of the fetus and neonatal infant afford an increased oxygen carrying capacity in the same manner that these conditions are known to operate in adults with certain types of congenital defects of the heart. Finally, the infant does not indulge in physical activities of a type which put a sustained excessive demand on oxygen intake until

ample time has elapsed for readjustment to postnatal conditions. There is, in brief, no functional exigency that forces us to postulate a violent postnatal increase in the volume of the pulmonary circulation. That there is some immediate acceleration of flow under the influence of the massaging effect of respiratory movements seems highly probable. But the radical increase in the volume of circulation necessary even to approximate an equalization of left with right atrial intake must await the gradual enlargement of the pulmonary channels in response to functional activity. Just how long a time elapses before such equalization takes place we can know with exactness only when there are available critical pressure determinations for both fetal and neonatal circulation. There are already known, however, several facts which fit together to give us a suggestive picture. These are:

1. The closure of the ductus arteriosus is a gradual process depending upon histological changes resembling those of endarteritis obliterans (Schaeffer,[13] 1914). Commencing at the time of birth there is a gradual reduction in the bore of this vessel culminating in obliteration of its lumen not earlier, on the average, than six to eight weeks after birth (Scammon and Norris,[12] 1918). This progressive occlusion of the ductus arteriosus by a process as characteristic and regular as the prenatal growth of the cardiac septa,* would tend to aid in the gradual enlargement of the pulmonary circulation by diverting a progressively greater amount of blood to the lungs.

2. In the heart of an unborn term fetus examined under water, the valvula foraminis ovalis does not lie stretched in close apposition to the interatrial septum but balloons out toward the left atrium in a position which shows the influence of the prenatal blood flow from right to left (Fig. 1). This characteristic configuration is lost gradually during the first postnatal month in a manner strongly suggestive of a gradual cessation of interatrial flow paralleling increase in pulmonary return. Measurements of the functional interatrial orifice made with a calibrated cone show a progressive reduction in its size following the "taking up of the slack" in the valvula and culminating with complete anatomical closure rarely earlier than from six to nine months after birth. Furthermore a distinct histological alteration in the valvula accompanies these changes. At birth the valvula is composed almost entirely of muscle with just a thin endocardial investment. Beginning two to three months after birth there is an exceedingly rapid increase in fibrous

*That the occlusion of the ductus arteriosus is an active process is indicated by the fact that prodromal histological changes in its intima are not uncommonly recognizable in fetuses which died without breathing and consequently never were subjected to the influence of postnatal living conditions, and further by the fact that the ductus sometimes closes in individuals with congenital defects of the heart of a type in which the persistence of the ductus arteriosus would obviously increase the chances of survival. Its frequent persistence in aortic or pulmonary stenosis seems to indicate merely that it is possible for a blood current of sufficient power to offset the normal tendency to closure. Failure of the ductus to become obliterated in the absence of some obvious cause is extremely rare, much rarer than primary developmental arrests of the cardiac septa.

tissue which by six months has increased 500 to 600 per cent, while there is in the same period no appreciable increase in the muscle tissue (Patten,[6] 1930). These changes at the foramen ovale clearly imply its gradual abandonment concurrently with the decrease in bore of the ductus arteriosus and the increase in pulmonary circulation.

3. The lungs of neonatal infants coming to autopsy characteristically show incomplete inflation. The lungs appear to come into full functional activity but gradually, the atelectatic areas becoming progressively smaller until complete inflation is reached normally about the third postnatal week.

4. The high red cell count and the high hemoglobin index characteristic of the fetus and neonatal infant rapidly decrease during the first month after birth (Japha,[2] 1908). This decrease probably parallels the increase in volume and efficiency of the pulmonary circulation.

5. The portion of the aorta between the origin of the left subclavian artery and the entrance of the ductus arteriosus ("isthmic portion") which, in the fetus, is characteristically narrowed (see Fig. 3) takes two months or more to widen to the bore of the aorta below the ductus. This seems indicative at once of a gradual cessation of ductus contribution to aortic current, and of a gradual gain in the power of the blood stream delivered by the left side of the heart to the aortic arch proximal to the narrowing. This in turn must depend upon the progressive increase of pulmonary return to the left atrium.

With full recognition that until pressure determinations are available for the fetal and neonatal circulation the evidence is incomplete, it can nevertheless be stated that all the facts now available point to the conclusion that the changes in circulation following birth are gradual rather than abrupt. As nearly as it can be sketched out at present the transition from fetal to neonatal circulation seems to occur thus: By the time of birth the fetal pulmonary circulation has developed to a point such that it is capable of supporting life as soon as the lungs are ventilated. After birth, under the stimulus of the functional activity of the lungs, the pulmonary circulation rapidly gains in power and volume. It is quite possible that the progressive reduction of the ductus arteriosus is normally a contributing factor in this increase in pulmonary circulation, but the increase can be—and not infrequently is—attained in cases where the ductus remains unclosed. By the end of the first or the beginning of the second postnatal month the pulmonary return to the left atrium has reached approximate equivalence with the right atrial return. When this has occurred, the foramen ovale falls into disuse as an equalizing short-cut between the pulmonary and systemic sides of the circuit. Its anatomical obliteration follows leisurely in the wake of its functional abandonment.

In the absence of actual structural defects of the valvula which make it inadequate to occlude the foramen ovale, delay in its fairly complete closure should be regarded, not as a cause of circulatory incompetence, but as a result of failure successfully to attain the new functional equilibrium characteristic of postnatal life. For example, practically all of the many recorded cases of true congenital pulmonary stenosis show retention of a widely open foramen ovale. Failure of absolutely complete fibrous adhesion of a functionally competent valvula should be sharply distinguished from a freely open condition of the foramen ovale. Failure of complete adhesion is very common (±20 per cent of all adults) and appears to be of no functional significance provided the valvula completely covers the septal orifice, and there is no complicating abnormality elsewhere in the cardiovascular mechanism.

The establishment of the new functional balance in the heart and the closure of the fetal communications between the pulmonary and systemic circuits carry in their wake changes in the relative development of right and left ventricular musculature. In the fetus with its open ductus arteriosus the load of the systemic circuit is shared by the right and left ventricles, and their muscular walls are of about the same thickness, although the total bulk of the right ventricle is a little greater because of its slightly greater capacity. By three to four months after birth the left ventricular musculature has overtaken the right in response, first, to the progressively increasing return from the lungs; then, as the fetal passages become closed, to the added stimulus of the long systemic route over which the blood must be pumped by the left ventricle alone. In response to this added load the left ventricular weight begins to climb steadily above that of the right, until its full adult degree of preponderance is reached somewhere around the seventh year (Müller,[5] 1883, Gross,[1] 1921).

SUMMARY

On the basis of the evidence at present available, the changes in circulation which take place following birth may be summed up as follows:

1. Current conceptions as to the occurrence at the moment of birth of an abrupt rerouting of the blood in the heart and great vessels rest on insufficient evidence.

2. There is an increasing reason to believe that the volume of blood circulating through the lungs at the close of fetal life is adequate to care for the respiratory demands of the newborn infant as soon as the lungs are properly ventilated, and that no radical circulatory upheaval occurs at the time of birth.

3. In the neonatal period, with the assumption of respiratory function, the volume and power of the pulmonary circuit gradually in-

crease, bringing about, by the close of the first month, a new functional balance in intracardiac pressure.

4. It is probable that under normal conditions the progressive closure of the ductus arteriosus accelerates the enlargement of the pulmonary vessels following birth, but there are many cases on record where a normal pulmonary circulation has been established without closure of the ductus.

5. With the establishment of the new interatrial equilibrium brought about by increase in pulmonary circulation the foramen ovale falls gradually into disuse.

6. Anatomical obliteration of the foramen ovale follows slowly in the wake of its functional abandonment. Provided the valvula foraminis ovalis competently covers the foramen ovale, failure of the valve completely to fuse to the septum is no functional handicap as long as there is not an intercurrent disturbance elsewhere in the cardiovascular mechanism or in the lungs. This fusion is incomplete, leaving what might be termed a "probe-patency" in about 20 per cent of all adults. Functional incompetence of the valvula by reason of defective development, which should be clearly distinguished from "probe-patency," is as uncommon as other cardiac anomalies.

7. Failure of the ductus arteriosus to close within the normal time range is to be regarded as a symptom rather than a cause of circulatory disfunction. Instances of the ductus remaining unclosed in the absence of abnormal conditions which force the maintenance of a blood current through it are exceedingly rare.

8. Following the increase in pulmonary circulation and the closure of the fetal blood passages there is a gradual increase in the left ventricular musculature to equal the right at about three to five months, acquire a definite preponderance by the second year, and its full adult degree of preponderance by about the seventh year.

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THE REVERSAL OF FLOW IN THE CARDIAC VEINS*†

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THE problem of the actual irrigation of the myocardium has been overshadowed by the study of the anastomoses of the coronary arteries. Interarterial connections are significant only in cases of partial or total occlusion of a single coronary artery; their significance completely disappears in double coronary occlusion. With this condition, with the arterial supply shut off, patients can live for a number of months, perhaps for two years.[4, 19, 22, 34, 44] Hypotheses, centering about irrigation by the Thebesian veins, or about anastomoses with the vasa vasorum, have been advanced to account for this persistence of life. The hypotheses are unsatisfactory either because they have been arrived at by a process of exclusion (which, as we shall show, has not been completely carried out), or because they are based upon experiments with isolated hearts.

In our study we have sought to obtain definite, direct evidence in the intact animal toward answering the question: How are the myocardial capillaries irrigated?

To make clear our point of view in discussing these experiments we will first present our concept of the vascular systems of the myocardium. In the light of our own experience in the study of anatomical specimens, as well as in the light of our experiments, we have essayed the following correlation and interpretation of the facts of the myocardial circulation.

THE MYOCARDIAL CIRCULATION

The exact anatomical peculiarities of the vascular bed of the heart are still not fully determined. The elementary notion of a small artery ending in a capillary bed and this in turn drained by a small vein is here entirely out of place. To begin on the arterial side, the question of anastomoses has been most confusing. These anastomoses have been found, confirmed, denied, and confirmed again. At present the work of Spalteholz,[38, 40] Nussbaum,[31] and of Gross[9] definitely establishes the presence of these anastomotic connections. The exact maximum of size of these connections we feel to be still in doubt because the intrin-

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sic contractility and the passive distensibility of the vascular tree interfere with determining the size of the communications from anatomical specimens, whether these be injected preparations or sections.

In addition to these intracardiac anastomoses we must also consider the extracardiac ones. The paper by von Langer[23] gives what seems to be the most complete account of these. In considering occlusion of the coronary arterial ostia, the most important extracardiac connection seems to be the communication between the coronary arteries and the bronchial arteries through the capillaries of the vasa vasorum of the first part of the aorta. In some of the reported cases the occlusion of the ostia of the coronary arteries has been accompanied by an obliteration of the lumina of the arteries for some distance from their origin. In these cases the extracardiac anastomoses with the bronchial arteries could not operate. The capillary bed in the region of the sinuses of Valsalva is so small that it does not seem possible that such anastomoses could nourish more than a small fraction of the myocardium. No doubt the extracardiac supply of the human heart could be restudied with profit, especially if such studies were correlated with the comparative anatomical studies of Grant and Regnier.[7] Since the lumina of nonfunctioning vessels are commonly obliterated, even when the vessels are not involved in a pathological process, it would be most helpful to have a complete description of the entire coronary arterial tree in the cases of double coronary occlusion. Arteriovenous anastomoses, to our knowledge, have not been recognized under that classification* in the heart, except by Nussbaum.[31] He believes that this system, which he found in the epicardium, serves to transmit blood from the arteries to the veins during systole when the capillaries are contracted. The general distribution of the arteriovenous anastomoses was first described by Hoyer.[13] The widespread presence of this connection is now well established. It is not surprising to find this anastomosis developed in the heart.

On the venous side we may divide the larger vessels into those which empty into the coronary venous sinus and those which empty into the right atrium directly. The coronary sinus has valves, the veins which empty directly into the right atrium do not. Since the influence of the valves of the coronary venous sinus can be discounted[32, 46] in 97 per cent of the cases, there does not seem to be any essential difference between these two classes of veins. Grant and Regnier[7] think that these various veins are present as an incomplete transformation of the primordial extracardiac venous drainage. The congenital anomalies of connection of the veins do not concern us in this present discussion,

*Halpert[11] reports what seems to be an unique case of a cardiac arteriovenous aneurysm. "The anastomosing loop shows a microscopic structure intermediate between an artery and a vein. Anatomically, the malformed vessels constitute a direct and relatively wide communication between aorta and right atrium; it is remarkable that such a striking abnormality was not associated with obvious disturbance of the heart during life."

for they too are the persistence, for the most part, of remnants of an extracardiac drainage. Intervenous anastomoses are of large size and of frequent occurrence. They are readily recognized with the naked eye.

There is a third group of vascular channels, the components of which have commonly been considered as unrelated structures, or these components have been divided into more groups than we feel is warranted. In fact, a group classification is rarely used. These channels were recognized in part and described by Vieussens in 1706[43] and by Thebesius in 1708.[41] Other varieties of the channels have been described by von Langer,[23] Lannelongue,[21] and others. Some observers, who have not seen all of the subtypes, have denied the existence of certain of them. This has added to the confusion. It seems to us to be significant that the multiplicity of terms and of descriptions sprang up at a time antedating the study of the embryology of the heart. Considering the work of Minot,[29] of Lewis[25] and of Grant and Regnier[7] on the development of the sinusoids of the heart the conclusion seems compelling that these variously described channels of the adult heart represent various stages in the evolution of the embryonic (and comparative anatomical) sinusoidal system of irrigation of the myocardium. Lewis,[25] believing that he found obliteration of some of the sinusoidal vessels in the embryo, thought that the endothelial channels might be formed in part by ramification of new vessels. Grant and Regnier,[7] on the other hand, have been unable to confirm this obliteration of the sinusoidal channels. We fail to see the analogy between the vasa vasorum and the endocardial vessels suggested by Lewis, and are of the opinion that all of the vascular passages of endocardial origin are modified sinusoids. According to this conception, based on development, on comparative anatomy, and on comparative physiology, all of the endocardial channels in any chamber: the blind pits, the communicating pits, the branched channels, the arborizing channels and those channels connecting with the capillary bed, are all parts of the sinusoidal system. It is true that certain of these have been called Thebesian veins (the *venae cordis minimae* of the BNA.) but there has been no agreement among authors as to what should be included under this term, and we have found authors using the term in a restricted sense in one paper and in an amplified sense in another. Some investigators, Pratt,[34] Wearn[44] and Kretz,[19] for example, feel that in cases of coronary occlusion the direction of flow is away from the cavities of the heart. In view of the embryological and comparative anatomical background of these vessels, and in view of their uncertain physiology, we feel that the term "vein" should be dropped, that the entire group of crypts and vessels should be referred to as the sinusoidal circulation of the heart, or if this does not meet with approval, to alter the term from *venae cordis minimae* (BNA) to *vasae cordis minimae*. In

this paper we shall refer to all vessels of endocardial origin as sinusoidal vessels. We shall not use the term, Thebesian vein, which we consider unsatisfactory.

So far as the embryology of the vessels of the heart has been worked out, the various circulations appear in the following order: The irrigation of the myocardium is first accomplished by the sinusoidal circulation; next the veins grow out and arborize; last of all, the arteries grow out and meet the capillary ramifications of the veins, and all three, sinusoids, veins, and arteries, become intimately connected through the developing capillary bed. So much of our knowledge of embryology has been accomplished through the study of stereotyped stages that we are inclined to overlook embryonic physiology. In the rabbit embryo, the veins exist as an independent system for days. With the pressure changes at their ostia, with the movement of the heart into which they are distributed, and with the presence of blood in their lumina, we feel that a flow and ebb circulation takes place in the veins during this period of their independent existence. This flow and ebb no doubt also occurs in the arteries before they join the veins but, because of the greater pressure, the degree of flow and ebb is probably less.

Considering the origin and early history of the sinusoidal system rich communications should be expected, not only with the capillaries, but also with the arteries and veins. Both Lewis[25] and Grant[6] feel that some of the capillaries are formed by a reduction in size of the sinusoidal channels. The connections with the veins have long been recognized and recently have been well demonstrated in anatomical preparations of the heart of the sheep by Grant and Viko.[8] Connections between the arteries and the sinusoids were demonstrated by injection experiments with coarse masses by Abernathy in 1798.[2] Mettier, Zschiesche and Wearn[28] prepared anatomical specimens by corrosion which show these vessels connecting the arteries and the sinusoids. We propose to call these two (at present unnamed) connections respectively, sinusoidovenous and sinusoidoarterial anastomoses.

In summary of the foregoing review we present Fig. 1, which shows in diagram form our concept of the anatomical facts and surmises of the myocardial circulation.

The lymphatic vessels have not been included in this discussion because their drainage is extracardiac. We have seen one incomplete specimen (in the dog) in which the possibility of the connection of a large lymph vessel with the veins could not be ruled out, but if this be present it is certainly the exception.[16] The amount of fluid leaving by these passages during perfusion of a heart, so far as we know, has not been determined. Considering the richness of distribution and the great size of the channels, this quantity must be quite large. In-

deed, Pratt[34] has suggested that the lymph channels may be concerned in the myocardial nutrition.

The study of the anatomical size and distribution of the components of the myocardial circulation by customary means is open to all the difficulties and objections encountered elsewhere in the animal organism, as well as to one peculiar to the heart. The passive distensibility of vessels has already been mentioned as well as their intrinsic contractility. We recognize, especially as a result of the work of Krogh[20] and of Richards,[36] that certain vessels may be temporarily contracted to the point of obliteration, while neighboring ones may be carrying a full stream of blood. This intrinsic contractility of vessels in localized areas, while it has not been specifically demonstrated in the heart, is no doubt active there and may explain in part some of the discrepan-

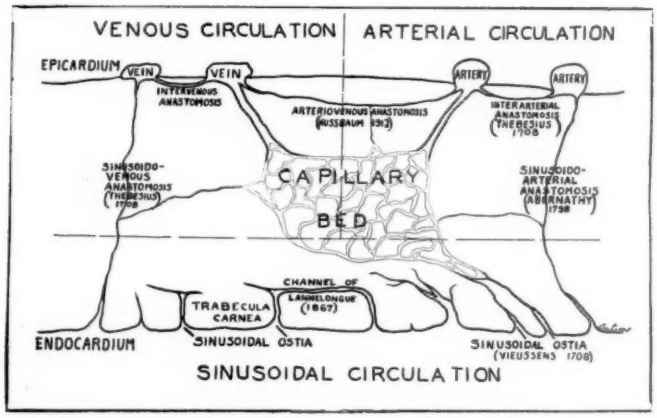

Fig. 1.—Diagram of the myocardial circulation. This diagram is based upon the embryological origin and the adult distribution of the vessels and the terminology employed is compatible with these points of view and with the terminology generally employed in the vascular system. In development the endocardial sinusoidal system develops first; the epicardial venous vessels develop next, and finally the epicardial arterial vessels develop and join the other two, forming a common capillary bed. The endocardial or epicardial origin of the vessels as well as their various modes of interconnection are indicated in the diagram.

Sinusoidal ostia are present in all four chambers of the heart.

Intervenous anastomoses have long been common knowledge. They are obvious with the naked eye.

Sinusoidovenous anastomoses have been recognized by Thebesius (1708),[41] Verheyen (1712),[42] Lancicius (1740 [posthumous])[23] von Haller (1786),[10] Abernathy (1798),[2] Bochdelak (1868),[3] (von Langer (1880),[23] Pratt (1898),[34] Nussbaum (1912),[31] Kretz (1927),[19] Wearn (1928)[44] and Grant and Viko (1929).[8]

Sinusoido-arterial anastomoses were described by Abernathy (1798)[2] and by Wearn (1928).[44]

Arteriovenous anastomoses were described and figured by Nussbaum (1912).[31]

Interarterial anastomoses are reported by Thebesius (1708),[41] von Haller 1786),[10] Morgagni (1761),[30] Senac (1749),[37] Caldani and Caldani (1810),[5] Krause (1879),[18] Jamin and Merkel (1907),[15] Spalteholz (1907)[38] and (1924),[40] and by Gross (1921).[9]

Sinusoidocapillary connections are recognized by Vieussens (1706)[43] Thebesius (1708),[41] Winslow (1776),[46] Verheyen (1712),[42] Lancisius, (1740),[24] Bochdelak (1868),[3] Henle (1880),[12] Hyrtl (1884),[14] Langer (1880),[23] Gross (1921),[9] and Grant and Viko (1929).[8]

cies obtained through the study of injected specimens. In the heart, in addition to the difficulties met with elsewhere in injecting the vessels for study, the vascular bed is constantly modified by the contrac-

tion and relaxation of the muscle itself. In dead hearts, after the effect of rigor mortis has disappeared, post-mortem changes have altered the distensibility of the vessels and have also impaired the integrity of their walls. Fixation and subsequent treatment further alter the validity of size determinations.

Experiments with perfused hearts are open to the objection that the heart is not actually performing work.* The vascular tree is being deformed by the contraction of the myocardium, but the resistance to the outflow of vessels is not present. This type of experiment has been most useful, however, in indicating that, with vessels conducting fluid in a given direction, the heart beat can be maintained. Pratt has shown,[34] for example, that the heart beat can be maintained by irrigation of the sinusoidal vessels and also that the beat can be maintained for an even longer period by irrigation of the coronary veins. Considering the absence of adequate valves in the cardiac vascular system and considering the connections indicated in Fig. 1, this is readily understandable; for, as we pointed out earlier, the capillary bed is the essential part of the circulatory system. It must be here emphasized, however, that these experiments demonstrated the possibilities of perfusion in certain directions, without indicating that these directions of flow actually occur in the intact organism. In the cases of double coronary artery occlusion, Wearn,[44] Leary and Wearn,[22] and previously Pratt[34] and Kretz[19] have advanced the explanation that the capillary bed received blood entering the sinusoidal vessels from the heart chambers. Leary and Wearn state: "The only adequate explanation of the ability of these patients to live and work rests upon a belief that the Thebesian veins have supplied the compensatory circulation necessary for the functioning of the heart muscle." This conclusion seems to be commonly arrived at by the process of exclusion; however, this mode of irrigation has never been demonstrated in the intact animal.

With these occlusion cases in mind, as well as the suggested explanation, we decided to approach the problem directly by trying to follow the course of particles injected into an intact animal. In order to eliminate the coronary arteries from the field of distribution we proposed to introduce particles into the systemic venous circulation, of such a size that they would be filtered out by the lung capillaries. This gave us the opportunity to investigate all of the vessels having ostia in the right side of the heart. Any particles appearing in the myocardial circulation would of necessity have entered through these ostia, ostia which include the openings of both the venous and the sinusoidal circulation.

*To quote Pratt[35], in discussing his own experiments: "Too much must not be inferred from such a demonstration for the heart is working against practically no resistance."

In retrospect, we can divide our experiments into three groups, which follow each other chronologically. A sufficient number of experiments from each group will be here reported in detail to show the character of our findings. Our first experiments were concerned with finding a suitable injection material. Dogs were used as experimental animals.

FIRST GROUP OF EXPERIMENTS

Unfortunately, there are no particles which have been standardized for use in injection experiments. For our first experiment we tried the glass particles which are sold for the purpose of "frosting" objects for decoration. These are smooth glass particles, like beads without perforations, with a diameter ranging from 200 to 600 micra.

EXPERIMENT 1.—October 25, 1928. Dog under amytal anesthesia. The right external jugular vein was exposed and a cannula ligated in place. A 50 c.c. syringe was filled with a "suspension" of the above described glass beads in normal saline. These were rapidly injected to prevent settling. This was repeated (total 100 c.c.). The animal expired seven minutes after the termination of the injection.

Findings.—Roentgenograms of the thoracic viscera showed extensive filling of the pulmonary vascular tree. Glass bead shadows were found singly and in clusters in the nonseptal portion of the right heart and in the interventricular septum. No bead shadows were seen in the nonseptal portion of the left heart.

Direct Examination.—The heart, which was markedly dilated on the right side, was opened and examined grossly, and with the binocular microscope (Greenough type). Large masses of fibrin, containing enmeshed glass beads were found in the right ventricle. These strands were especially numerous in the crypts between the columnae carneae. No beads or fibrin strings were found in the left heart. In two instances beads were found within sinusoidal orifices in the right ventricle.

Discussion.—The difficulty of retaining the beads in suspension suggested that a lighter particle would be more suitable. The dilated right heart and the filled pulmonary vascular tree indicated that death was due to the pulmonary embolism with the resulting fall of pressure in the left heart and in the coronary arteries. This condition then, simulated to a great degree an acute coronary occlusion.

EXPERIMENT 2.—November 1, 1928. Because of its availability in graded sizes we decided to use carborundum powder in our next experiment. We used the grade FFF, which was prepared by repeated washing with saline solution. After each washing the finer particles were removed by decantation.

Procedure.—With the dog under amytal anesthesia 100 c.c. of FFF carborundum powder suspension were injected into the right external jugular vein. Within two minutes after the beginning of the injection breathing ceased, and the animal went into an extension rigor. The heart beat could not be heard. The chest was immediately opened, the great vessels were ligated, and the heart and lungs were immediately removed.

Findings.—The lungs showed a patchy grey discoloration which on close inspection was seen to be carborundum. Grossly, the veins of the entire heart contained carborundum. Inspection of these vessels under magnification and dissection showed the coronary venous sinus and its tributaries to be well filled. On opening the heart, the right side was found filled with a large, firm, carborundum containing clot. The carborundum was found chiefly on the periphery. Some extensions of the clot into crypts came loose when the clot was washed out. The

ostia of the sinusoids were well filled with the particles. The specimen was fixed in formaldehyde solution and then cleared by the Spalteholz method.[39] Upon examination of the cleared specimen the findings noted above were confirmed. Carborundum was not found in the left heart.

Discussion.—The finding of particulate matter in the superficial cardiac veins indicated the surprising fact of a reversal of flow in these vessels. We determined to investigate the influence of the massive clot and the dilated right side of the heart on this reversal. It was considered highly possible that the conditions of the experiment were so unusual that they were not only outside of normal circulatory conditions but also outside of pathological ones. Further, the introduction of the material with a syringe so near the heart might have caused a direct injection.

EXPERIMENT 3.—November 6, 1928. The conditions of the last experiment were duplicated except that particulate matter was introduced into the right femoral vein in order that the venous pressure might be less disturbed. The findings were in all respects the same, including the finding of carborundum in the coronary veins. Apparently the reversal of flow in the preceding experiment had not been caused by the pressure of injection.

Our next experiments were directed toward finding a means of eliminating the massive clots formed by the carborundum.

SECOND GROUP OF EXPERIMENTS

It was suggested to us by Dr. G. M. Higgins of the University of Minnesota, that colloidal graphite might be a satisfactory substance, and that, in his experience, clots did not form when it was used. We found that the particles of the colloidal graphite were too small for our purposes, but we decided to try commercial flake graphite.

EXPERIMENT.—April 10, 1929. Fine, flake natural graphite commercially obtained was prepared with physiological salt solution. The finer particles were removed by decantation and by the use of a centrifuge. A medium sized dog under amytal anesthesia was used. A gravity tube ligated in the right femoral vein was used for the injection. The graphite suspension was introduced at a maximum pressure of 12 centimeters of water. Twenty cubic centimeters were introduced after which, either due to a plugged cannula or to the failing heart no more would run in.

Findings.—No graphite was seen upon opening the abdomen. Upon opening the thorax the right side of the heart was found to be distended and firm. No graphite could be seen grossly in the lungs. On opening the heart dense clots were seen in both sides. Graphite was found only in the right side. Graphite was found in the coronary venous sinus and in the coronary veins. Graphite was found in smears from the lungs. None was found in the clot from the left heart, and none was found in smears of the splenic pulp.

Discussion.—The graphite seemed to be a better substance to inject than the carborundum, but it caused coagulation in its commercial flake form. We decided to continue the use of graphite but to try the use of an anticoagulant.

The effect of the injection of peptone solution was tried but the results were not completely satisfactory. Following this we turned to heparin.

Considering the acute nature of our experiments we felt that a smaller dose than recommended would probably suffice.

EXPERIMENT.—April 27, 1929. Dog was placed under amytal anesthesia. A gravity cannula was ligated into the right femoral vein. Fifty milligrams of heparin

per kilogram of weight were injected intravenously, and thirty minutes were allowed to elapse. The absence of the clotting of the blood was determined by making skin incisions and mixing graphite with the exuding blood. Thirty-five cubic centimeters of a graphite suspension were injected at a pressure of 110 mm. of water. Respiration ceased in two minutes.

Findings.—The cardiac blood was not clotted. Graphite was abundantly present in the coronary veins and in the cardiac veins.

Discussion.—In this experiment the injection of the cardiac veins was due neither to the height of the injection pressure nor to the massaging action of the clot. Up to this time the pressures present in the right atrium of the heart and in the arteries had not been determined; however, gross observation showed them to be quite abnormal. This lack of information brought us to our third set of experiments. Here we endeavored to determine these pressures in the right side of the heart, and to bring them within normal ranges.

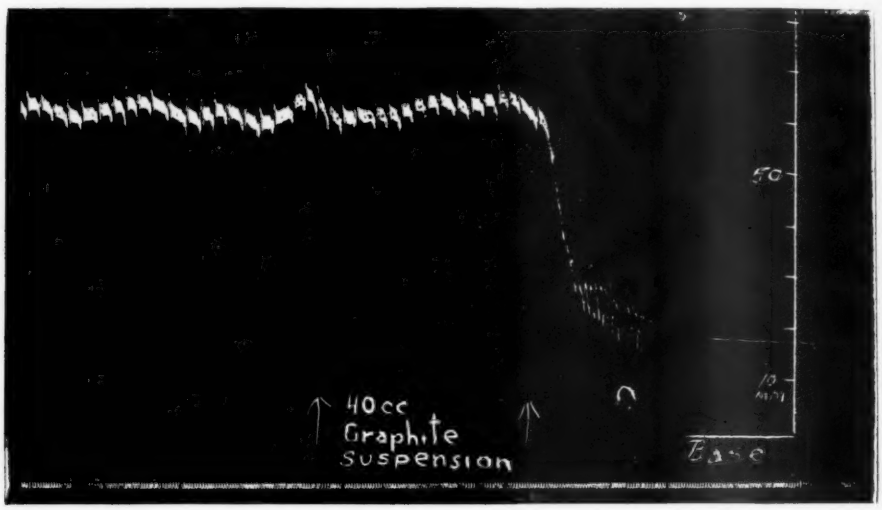

Fig. 2.—Tracing of pressure in the left carotid artery. Experiment, December 3, 1929, at the time of injection of the graphite suspension into the systemic veins.

THIRD GROUP OF EXPERIMENTS

EXPERIMENT.—Carotid pressures. December 3, 1929. The conditions of this experiment duplicated those of the one last recorded except that the necessary apparatus was arranged to record the carotid pressure. The injection pressure was 12 cm. of water. The animal ceased breathing shortly after the injection of the graphite suspension (Fig. 2). Graphite was found in the heart as in the previous experiments.

Discussion.—The figure of the blood pressure curve (Fig. 2) is characteristic of others that we obtained later. This shows the extent to which the coronary pressure was reduced and also the height of the residual pressure, in these experiments.

In order to determine the pressures in the right atrium or its superior entrance, a water manometer was used, to which a cannula long enough to reach the heart was attached.

EXPERIMENT.—December 10, 1929. Dog was placed under amytal anesthesia. A gravity injecting cannula was ligated into the right femoral vein, and heparin was

administered. A cannula, inserted into the left carotid artery, was connected to a recording manometer. The right external jugular vein was isolated. A glass tube, paraffin coated internally, as an additional precaution against clotting, was inserted into the right external jugular vein, toward the heart, for a distance of sixteen centimeters. The tube contained sodium citrate solution, and the free end was connected to the water manometer. Part of a fifty cubic centimeter quantity of a graphic suspension was introduced into the femoral vein at a pressure 5 cm. higher than the venous pressure at that point. The ensuing violent respirations caused such rapid shifts in the water manometer column that all of the levels could not be recorded. Fig. 3 indicates those readings that were recorded. Especially significant is the maximum figure of 43.5 cm. of water. The carotid tracing was in all respects similar to Fig. 1.

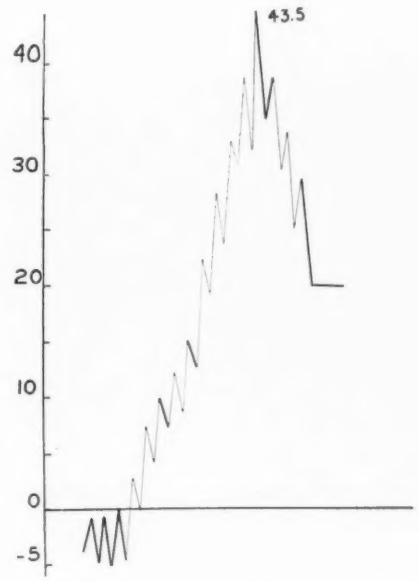

Fig. 3.—Experiment, December 10, 1929. Pressure in the right atrium during injection of a graphite suspension into the right femoral vein, toward the heart. The heavy lines indicate actual readings. The light lines are approximations. The figures are centimeters of water.

Findings.—The gross appearances of the heart is illustrated in Fig. 4. The presence of large quantities of graphite was much more obvious after the clearing of the specimen.

Discussion.—This experiment makes it clear that, in this vascular system with inadequate valves, a falling arterial pressure and an increased intra-atrial pressure results in a reversal of flow on the venous side.

As shown by Fig. 4 the particles are well distributed in veins of the left ventricle, remote from the right atrium. The question as to the minimum pressure in the right atrium necessary for this reversal was raised as well as the possibility of the direct inspection of the vascular tree.

EXPERIMENT.—December 12, 1929. Dog under amytal anesthesia. The thorax was opened by means of a saw cut splitting the sternum. Artificial respiration was carried out. Heparin was administered. The right coronary artery was ligated in

the coronary sulcus as well as two branches of the anterior descending ramus of the left coronary artery in order to produce a localized fall in coronary arterial pressure.

At this point direct inspection with a binocular magnifier, attached to a head band was attempted, in an effort to follow the direction of flow. The attempt was unsuccessful because it was not possible by this means to follow the flow in the rapidly moving heart and because localized immobilization was unsuccessful.

Next a cannula having a side outlet at 20 cm. was introduced directly into the superior vena cava. Thirty cubic centimeters of a graphite suspension were injected into the left femoral vein at a pressure 5 cm. above venous pressure.

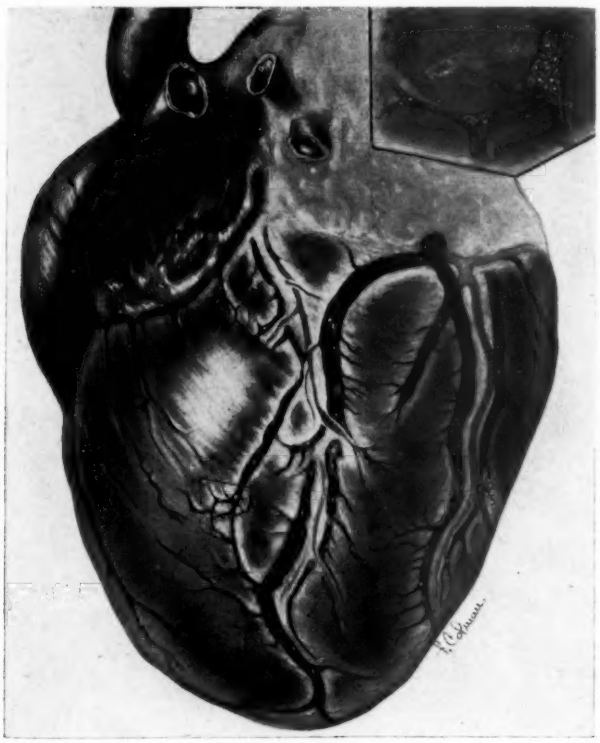

Fig. 4.—Dog's heart from experiment, December 10, 1929. Graphite particles are seen in the veins over the left ventricle. The inset shows a magnified view of the indicated area.

Pressure in the cannula in the vena cava rose to the 20 cm. outlet tube and about 10 c.c. spilled over. The outlet was closed, but the pressure did not rise above this level. The animal lived for three minutes after the graphite injection.

Findings.—The right heart was markedly dilated. The lungs contained graphite. The heart (Fig. 5) contained less graphite than the preceding specimen, but the distribution was similar.

Discussion.—The pressure here recorded, 20 cm. of blood, was much lower than the 43.5 cm. of water of the previous experiment. The difference between the two pressure readings was probably due to the opened chest. The experiment indicated that venous pressures within the range of pressures of pathological heart conditions could cause a reversal of flow in the heart veins.

The next experiment was planned so as to reduce or to eliminate the rise in intra-atrial pressure.

EXPERIMENT.—Dec. 19, 1929. Dog was put under amytal anesthesia. The gravity injection cannula was inserted into the left femoral vein. The right external jugular vein was isolated, preliminary to the introduction of a cannula. A large bottle partly filled with sodium citrate solution was connected by means of a syphon tube with a water manometer and a jugular cannula. The zero levels of the manometer and the syphon bottle were adjusted to coincide with the level of the right external jugular vein (Fig. 6). The animal was given heparin, and thirty minutes later 40 c.c. of a graphite suspension were introduced at an injection pressure of 5 cm. of water.

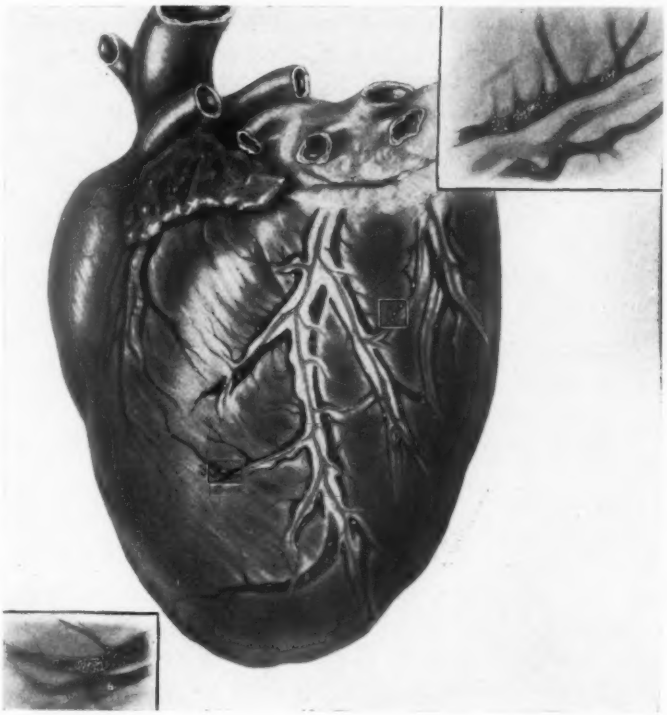

Fig. 5.—Heart from experiment, December 12, 1929. Distribution of particles indicating the extent of the reversal of flow in the cardiac veins with an intratrial pressure of 20 cm. of blood.

The pressure in the right atrium, as indicated by the manometer, rose momentarily to 11 cm. of water and then dropped rapidly to zero. (This rise may have been due to the inertia of the system, for the pressure drop to zero coincided with the arrival of the blood column in the equalizing bottle.) To relieve the respiratory embarrassment the equalizing bottle was lowered until the manometer reading stood at minus five centimeters. The breathing continued labored and the heart stopped beating.

Findings.—The thorax was opened. The cannula was found within the entrance of the left atrium. The vessels were ligated, and the specimen was removed. Graphite particles were seen in the fresh specimen in the veins accompanying the anterior descending branch of the left coronary artery (Fig. 7). This specimen was

later cleared and the further distribution of particles noted. Fewer particles were seen in this specimen than in previous ones.

Discussion.—This experiment carried out under lower pressure conditions—conditions which are within the limits of normality—shows that high pressures on the venous side are unnecessary for the injection of the veins in the presence of the falling arterial pressure.

The apparatus was modified by increasing the caliber of the tubing and shortening the length of the connections, in an effort to lessen the inertia of the system. A graphite suspension was carefully prepared, and the size of the particles was determined by the use of an ocular micrometer. The minimum diameters of one hundred measured particles ranged from 51 to 210 micra.

EXPERIMENT.—March 11, 1930. This experiment in all details duplicated the one last reported. Following the injection of 30 c.c. of the graphite suspension the pressure in the manometer did not deviate from zero. Blood appeared in the bottle, showing that the system was patent. The animal died about three minutes after the injection. The thorax was opened, the intra-atrial position of the cannula confirmed, the great vessels were ligated, and the heart was removed. Graphite particles were easily found in the veins. The specimen was fixed and later cleared by the Spalteholz method.[39]

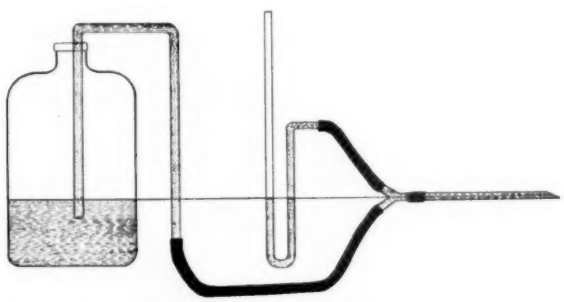

Fig. 6.—Arrangement of syphon bottle, manometer and jugular cannula in experiment of December 19, 1929. The zero level was adjusted to correspond to the level of the right external jugular vein.

Examination of the cleared specimen confirmed the presence of the graphite particles of the largest size in the heart veins and showed the left ventricle to be free of graphite.

Discussion.—In this experiment we feel that we have removed any question concerning the reversal of flow in the veins at normal pressure levels in the right atrium, when accompanied by a fall of pressure in the coronary arteries.

It was suggested that perhaps the presence of the sinusoidovenous anastomoses would account for the particles in the veins, without a reversal of flow being present. It is true that in some of the specimens from our experiments we had noted an injection of sinusoidal vessels, but we were never able in these to establish the continuity of a chain of particles from the sinusoids to the vein. In addition, because of the large size of the particles used, because of their presence in the veins of the left heart, and because of the great quantity present in all veins in certain experiments, we did not feel that this mode of injection was a possibility. However, to answer this type of objection we prepared a suspension of graphite from very large flakes. This was injected into an animal on April 8, 1930, according to our usual technic. The heart was removed and very carefully cleared by the

Spalteholz method, using certain procedures (which will be reported by one of us elsewhere) to develop the maximum clarity of the preparation. With this specimen in its finished state it has been very easy to study the vascular distribution and the presence of particles in the entire heart. It has been possible by the use of special illuminants, an arc lamp with a thick cobalt glass filter, to obtain what amounts to a selective illumination of a differential character, for the blood vessels. By careful study of the distribution and measurement of the size of vessels, using an ocular micrometer, we were successful in finding a vein containing large particles, that was so distributed anatomically, that the presence of large anastomoses could be ruled out. The connections were of such a small magnitude, that even if they included sinusoidovenous anastomoses the passage of the particles from sinusoids to veins would not be possible. We are fully cognizant of the known extrinsic

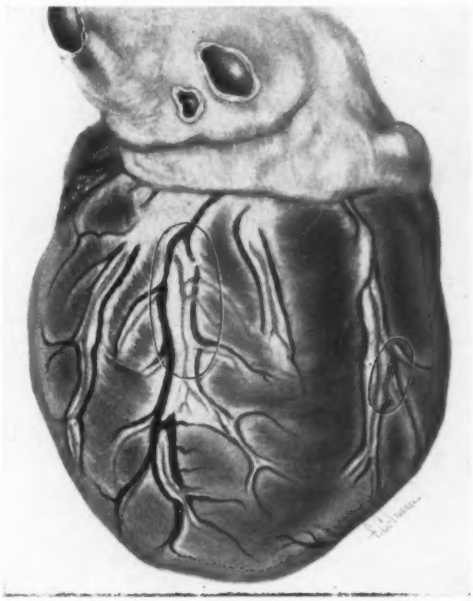

Fig. 7.—Heart from experiment of December 19, 1929. The reversal of flow in the cardiac veins is shown by the distribution of the graphite in the veins. The intra-atrial pressure reached a maximum of 11 cm. of water.

factors which alter the size of vascular lumina, we believe in the presence of an intrinsic alteration, and we appreciate the alterations, especially shrinkage of vessels caused by fixation, dehydration, and clearing, but we feel that the discrepancies in sizes here are too great to permit of any explanation, other than that the particles traveled into the vein in a manner exactly reverse to that which the blood is accustomed to follow. The largest particle is 800 micra by 1200 micra in this vessel and all of the arborizing (Fig. 8) vessels have been traced until their greatest internal diameter is less than one hundred micra. Fig. 8 is a composite illustration, made from camera lucida drawings. The diameters have been corrected to scale. The original drawings were made by rendering one tube of a Greenough type binocular vertical and attaching a camera lucida to this vertical tube. The other eye piece of the microscope was equipped with an ocular micrometer so that the measurements could be made. The illumination has already been mentioned. Focusing was accomplished by moving the specimen. It was necessary to make a series of draw-

ings because the vessel in question, one of the anterior cardiac veins, was followed from its ostium in the right atrium to its 200 micra anastomosing channels at the apex and then followed along the anastomotic vein until the direction of flow normal to this vein became apparent from the angles of fusion of the entering vessels.

PROBABLE MODE OF IRRIGATION IN CORONARY ARTERY OCCLUSION

Irrigation of the myocardium compatible with life, by venous blood, is not unknown (Abbott[1]). Furthermore, those that maintained that the sinusoidal circulation supplied the mode of irrigation in cases of coronary artery occlusion were offering an explanation that depended in part upon the use of blood from the right heart. It is easy

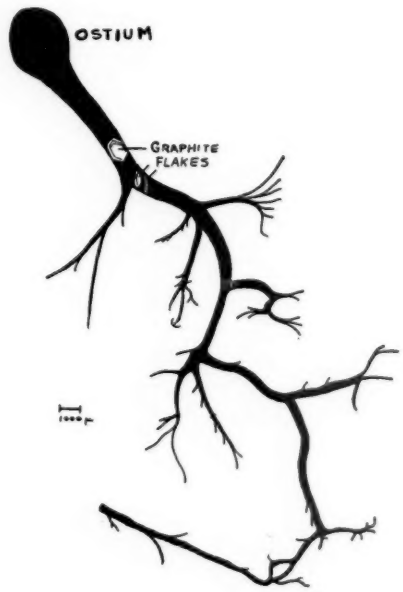

Fig. 8.—Camera Lucida drawing of the lumen of an anterior cardiac vein from the specimen obtained from the experiment of April 8, 1930. All of the connecting vessels with a diameter in the cleared specimen of more than 100 micra are delineated. The intervenous anastomosis in the lower part of the figure has a diameter of 200 micra. The largest graphite flake measures 800 by 1200 micra.

to understand how the myocardium can be maintained by venous blood when we recall that the oxygen tension of venous blood ranges from 60 to 70 per cent while the figure for arterial blood is 95 per cent.

In cases of occlusion of the coronary arteries we suggest that the blood passes into the veins at the time of atrial systole, it may flow in part through sinusoidovenous anastomoses into the ventricles as well as into the capillary bed. We believe that this blood is forced from the capillaries with the onset of ventricular systole. It is entirely possible that this blood reenters the heart chambers by two sets of channels, the veins and the sinusoids. The time periods of the heart cycle.

the rate of blood flow, and the length of the vascular bed make this flow and ebb explanation plausible. In some of our specimens, we have seen an injection of the sinusoidal ostia also. This may mean that blood also enters the capillary bed by these channels. Up to the present we have not endeavored to alter our experiments to evaluate the exact relationships between these two systems. There need be nothing incompatible in the idea that the capillary bed is supplied in both manners; although, if, as it is commonly thought, the ventricular sinusoidal vessels are filled during systole, it seems to us difficult to visualize how the capillary bed can be irrigated at this time when external pressure is greatest.

By considering the connections of the vascular system of the heart (Fig. 1) and by considering the absence of competent valves, the irrigation of the heart in coronary artery occlusion seems to us to become a simpler problem. The blood undoubtedly flows from vessels of greater pressure to vessels of lesser pressure. We realize that we have not determined the exact pressures involved, because we have not determined the effective pressures, i.e., the differences between the intra-atrial pressures and the intrathoracic pressures, under the conditions of our experiments, nor have we obtained intraventricular pressures to accompany these. These pressures no doubt will have to be determined and carefully compared before all of the ramifications of this problem are clear.

Again we mention the work of Pratt in 1898, showing that irrigation through veins was adequate for maintaining the perfused heart, and we also note that he considered this of sufficient importance to give it a subheading in his report. Porter,[33] in observing the hearts of cats and dogs recovering from fibrillary contractions, believed that this occurred through irrigation of the heart through the sinusoidal vessels and the coronary veins which were in a position peculiarly well adapted to function as a result of the pressure changes taking place in the ventricles during this state.

CLINICAL IMPLICATIONS

The myocardial capillary bed has three connections with the blood stream: the sinusoidal vessels, the veins, and the arteries (Fig. 1). Since the direction of flow in none of these vessels is determined by valves, we believe that it must be determined normally, and in any pathological condition met clinically by the pressures in the respective vessels, and by the obstruction to flow encountered. Our experiments support this view and indicate that in double coronary artery occlusion the flow is from the veins into the capillary bed. This irrigation by the venous system may be significant in other cardiac conditions.

The pain present in angina pectoris and in certain cases of localized coronary occlusion is usually regarded as due to an anoxemia of the

myocardium. This pain usually disappears with the inception of cardiac decompensation, with the onset of atrial fibrillation, or with the development of complete heart-block. Mackenzie[27] believes that shortness of breath so limits activity in these conditions that the patients are prevented from exerting themselves sufficiently to induce an attack of angina. This explanation has not been completely satisfactory (McCrae[26]). If we accept the current belief of the anoxemic origin of the pain, then, on the basis of our experimental findings, we are in a position to offer another explanation for the disappearance under the conditions just noted. In cardiac decompensation and atrial fibrillation there is produced an increase in the intra-atrial pressure which favors a reversal of flow in the veins with its resulting irrigation of the capillaries of the anoxemic areas.

In complete heart-block, especially with the inception of Adams-Stokes syndrome, the pressure relations are again such as to favor a reversal of flow in the veins with the resulting irrigation of the myocardium. During the periods of asystole the coronary artery pressure falls to an extremely low level. We suggest that the continuance of atrial contractions during ventricular standstill are largely responsible for cardiac irrigation, as a result of which the vitality of the myocardium is so maintained, that a succeeding, effective impulse causes restoration of the idioventricular rhythm. Instances of recovery from ventricular fibrillation have been reported in man.[17] In this condition irrigation of the ventricular muscle, by the coronary arteries is extremely unfavorable, but it could be easily attained by the reversal of flow in the heart veins.

SUMMARY

The myocardial capillary bed has three sets of connecting vessels. Named in the order of their embryological appearance and function these are: the sinusoidal vessels (in which are included the Thebesian Veins), the cardiac veins, and the coronary arteries. With the elimination of the arteries as in double coronary occlusion, the mode of irrigation of the capillaries has not been understood.

The direction of flow in the cardiac vessels joining the right heart was investigated under conditions simulating double coronary artery occlusion. Particles too large to pass through the lungs were injected into the veins, toward the heart, in anesthetized, heparinized dogs. These particles were uniformly found in the coronary sinus and the coronary veins. Their size was too great, and the arborizing and anastomosing veins were too small, to allow for any course of flow other than from right atrium to veins. The sinusoidal vessels (Thebesian veins) were excluded as a possible source of these particles in the veins, although irrigation of the capillaries in part, by them, was not excluded.

With a low pressure in the capillary bed (as in cases of double coronary occlusion or as in our experiments), flow in the veins during atrial systole is probably toward the capillary bed, the capillary bed being emptied during the ensuing ventricular systole. In arterial occlusion this would give a flow and ebb circulation for the myocardial capillaries by way of the veins.

This irrigation by venous channels may explain the disappearance of pain in angina pectoris, with the inception of those complications accompanied by a fall in the coronary artery pressure.

Most of the experiments for this study were carried out in the Department of Research Surgery. We thank Dr. I. S. Ravdin and his staff for the many facilities which they furnished us.

We are indebted to Dr. H. C. Bazett, Professor of Physiology, who reviewed our experiments.

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POSTURAL HYPOTENSION

A Case Report*

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POSTURAL hypotension was established as a clinical entity by Bradbury and Eggleston[1] in 1925 with a report of three cases. In 1928 two cases were reported by Ghrist and Brown[2] and two by W. T. Vaughan.[3] The following case makes eight now reported, but it is probable that the syndrome is much more common than the reports indicate.

The clinical picture now is well established and permits recognition of the disease from the history. The essential points are the complaint of dizziness upon changing the position of the body from supine to erect and the prompt relief of the dizziness by reassuming a reclining posture. This may vary from slight vertigo to actual fainting. The diagnosis is confirmed by blood pressure readings in the two positions.

Certain other associated symptoms seem sufficiently common to be included in the symptom complex. These are a marked pallor of the face during the attack with temporary blurring of vision and involuntary closing of the eyes. The hands and feet become cyanotic during the erect posture. There are also numbness, tingling, and slight convulsive jerking of one of the arms, frequently associated with sweating of the limb. The jerking movement is not unlike that seen in the Stokes-Adams syndrome or carbon monoxide poisoning, and might be mistaken for an epileptiform seizure should fainting occur. Weakness, ease of fatigue, and dyspnea on exertion are common. It has been noted that patients feel more uncomfortable during the summer months.

In all cases it is agreed that the basis of symptoms is a relative anemia of the brain due to lowering of the cardiac output in the erect position. There is no agreement in the cases reported as to the pathological change affecting this occurrence.

CASE REPORT

A native married American, aged sixty years, laborer, complained of diarrhea and dizziness gradually increasing for two years. The colitis disappeared following the use of a high vitamine diet and iodine, but the dizziness persisted until the patient was obliged to lie in bed constantly. On arising to the standing posture he immediately noted dizziness and a coarse jerking of the left forearm. The

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symptoms were alleviated somewhat by walking rapidly, but reappeared promptly upon standing still. The patient easily became short of breath upon exertion. There had been no loss of appetite. Dizziness was more pronounced in the morning following a bowel movement. While sitting quietly in a chair the patient often noticed increased sweating of the left side of the body.

Physical Examination.—Height 70 inches, weight 180 pounds. Sthenic habitus with rather wide costal angle, appearance and age coinciding. The patient was hyposensitive according to Libman's classification. Moderate emphysema. The vital capacity was 2300 c.c. or 55 per cent of the normal. The cardiac silhouette was of the aortic type but not definitely abnormal. There was general arterio-

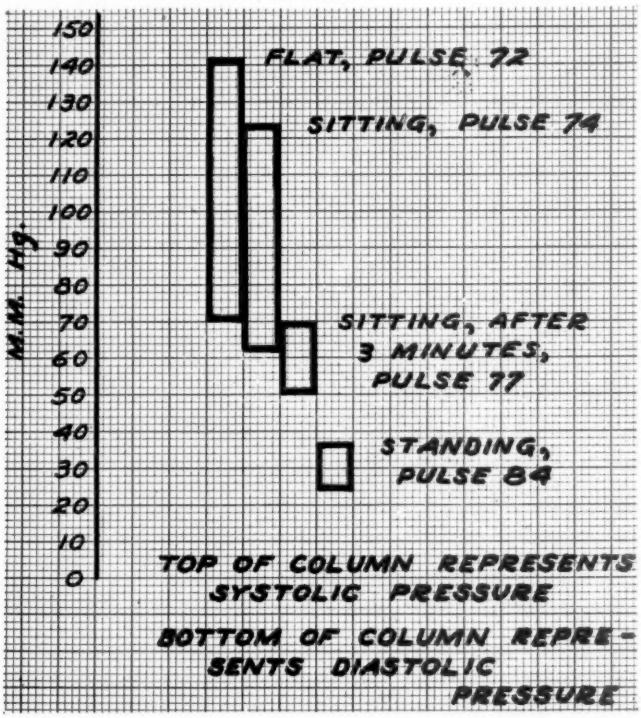

Chart 1.—Pulse pressures in the several positions.

sclerosis, and the retinal arteries showed moderate sclerosis. Blood pressure readings: right arm: supine 140/70 mm., sitting 70/50, standing 38/25, right leg (above knee): supine 235/70, sitting 212/80, standing 145/76.

Laboratory Data.—Urine negative. Peripheral blood normal. Electrocardiogram normal. X-ray studies of chest, gastrointestinal tract and skull negative. Labyrinthine tests normal. Basal metabolic rate −1 per cent (test satisfactory).

The following special examinations were directed toward the complaint: 0.3 c.c. adrenalin subcutaneously produced an increase in blood pressure to 200/120 mm. This was accompanied by a large number of extrasystoles and a sharp constrictive substernal pain. The patient became extremely sick and required the immediate application of amyl nitrite for relief, suggesting latent angina pectoris (Levine). However, dizziness could not be induced while the effect of adrenalin remained.

Phenolsulphoncphthalein Tests.—Supine excretion in two hours (intravenously) 35 per cent, sitting 11 per cent. In one case of Ghrist and Brown the phenolsulphonephthalein output was greater in the standing position. Blood pressure readings were taken by means of the Tycos recording sphygmomanometer in the various positions. In the erect posture besides the extremely low blood pressure the pulse pressure diminished to about 10-15 mm. mercury. When the patient was placed at rest with the head down, the blood pressure rose from 140/70 to 170/90 showing that the vasomotor center was unable to maintain the normal pressure in this position as well.

Studies on the heart were directed to show alterations in size with position by teleroentgenogram. No difference beyond the limits of normal could be demonstrated.

The water excretion test of Volhard was done in the two positions as a further study of the kidney circulation. In the supine position the output in four hours

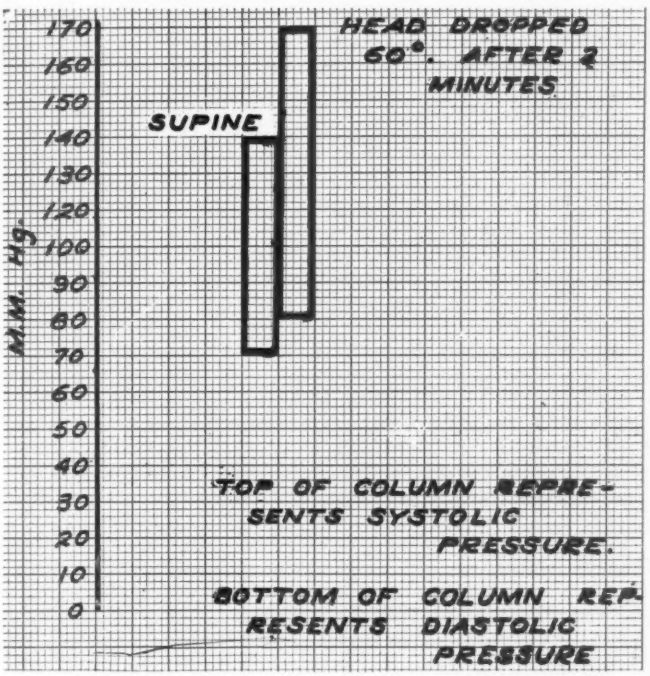

Chart 2.—Change in pulse pressure with head down.

was 1200 c.c. from an intake of 1500. In the standing posture it was 510 c.c. This test demonstrates (1) normal kidney function; (2) a deficient kidney circulation in the upright position; and (3) confirms the findings with the phenolsulphonephthalein tests.

The capillary blood pressures were done in the two positions using the finger tips. Pressure readings of 13 cm. of water were obtained in both positions constantly, by a trained observer. It was noted clinically that when the patient was standing the feet became cyanotic and that this subsided while the patient was walking.

Treatment with small doses of ephedrine (50 mg. twice a day) following the suggestion of Ghrist and Brown seemed only moderately successful, and with this the patient left the hospital, after one month's observation, not able to resume his occupation. The changes in blood pressure are shown graphically in Charts 1, 2, and 3.

COMMENT

This case is somewhat different from those reported by Bradbury and Eggleston in that there was no evidence of a thymolymphatic constitution. The blood pressure readings and the pulse pressures were lower in the reclining posture than in any of the seven cases previously reported.

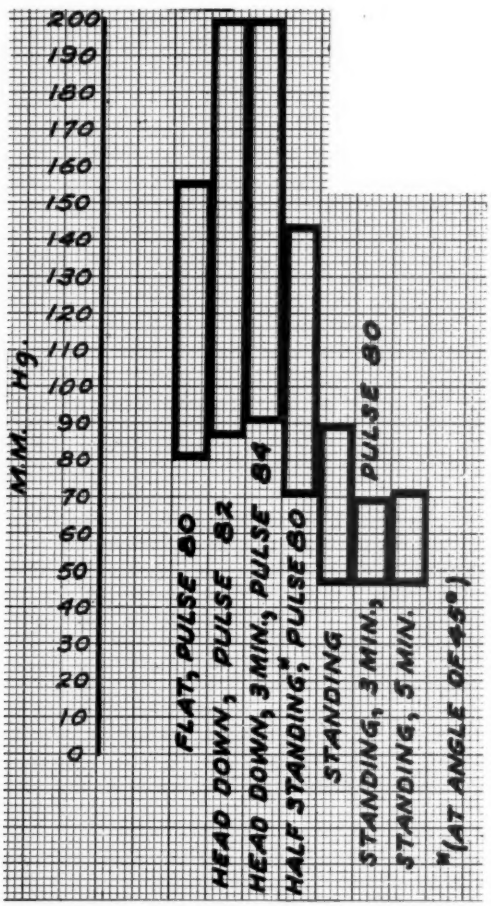

Chart 3.—Changes after use of 100 mg. of ephedrine (patient on table).

We can find no explanation of the underlying pathology in this case other than that the vasomotor regulating mechanism was incapable of responding in a normal manner to changes in position. This is shown by the fact that it failed to respond when the head was down as well as when the standing posture was assumed. It is suggested that the pathological lesion here might be that of cerebral arteriosclerosis with a special predilection to vasomotor mechanism. The experiments of Leonard Hill in 1887 explaining the changes in blood pressure with

posture on the basis of bleeding into the splanchnic area are difficult to confirm, and we are quite loath to accept these results as applying to this case or to the others in the literature, although a marked hydrostatic effect cannot be denied. There was no evidence of congestion of the kidneys on standing (casts, red cells and high water excretion) nor in any of the eight cases did increased abdominal pressure by bandage change the blood pressure. With the cyanosis of hands and feet, the marked decrease in kidney function, and the negative effect of abdominal bandage, it is obvious that there is a general rather than a splanchnic dilatation of the blood vessels in the erect posture.

That the peripheral vasomotor endings are intact is shown by the response to epinephrine and ephedrine.

CONCLUSIONS

A case of postural hypotension in an elderly man is reported in which arteriosclerosis and a lowered vital capacity were prominent findings.

The pathological physiology in this case seems to be a greatly reduced stroke volume of the heart induced by failure of the vasomotor nervous center to respond to the hydrostatic effect of the standing posture.

With the report of eight cases the clinical syndrome is well defined, and capable of recognition from the history.

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CARDIAC ANOMALY (SO-CALLED DOUBLE LEFT AURICLE)

Report of a Case*

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INTRODUCTION

THE heart is subject to more individual variations and anomalies than any organ in the body. The majority of these anomalies can be explained on an embryological basis. However, there are a few cases for which no adequate explanation has yet been offered. This case falls under the latter category. Cardiac anomalies can be divided into (1) viable and (2) nonviable. Many cardiac anomalies are not recognized until death, while others are recognized accidentally, and still others act as a primary factor in the cause of death early in life. There are innumerable classifications of cardiac anomalies, both clinical and pathological, but that of viable and nonviable seems best suited to this discussion.

CASE REPORT

History.—The patient, L. P., a male infant of three and one-half months, was brought to the University Hospital with a chief complaint of "trouble with the thymus gland."

Family History.—The mother and father were living and well. There were six other children, living and well; none were dead. There had been two miscarriages, one preceding the birth of normal children, the other following the birth of normal children. There had been no stillbirths.

Birth and Developmental History.—The child was born at full term; the delivery was normal and spontaneous. He was quite blue at birth. He weighed eleven pounds. There were no convulsions following delivery.

Present Illness.—The mother stated that the child had always been rather sickly, that he had diarrhea during the first five weeks of his life and had had intermittent attacks of difficulty in breathing, associated with cough and cyanosis. These attacks increased in frequency and severity as time went on. When the infant was five weeks old, the mother noticed a change in his voice. Previously it was normal in quality, whereas it changed to a high-pitched reedy note, suggestive of some obstruction in the larynx. At the onset, the cyanosis was noted only about the lips and nail-beds, only during the attacks of difficulty in breathing. As time went on, however, the child became constantly cyanotic. Two roentgen-ray treatments were given over the region of the thymus before the child was admitted to this hospital.

Course in the Hospital.—The child was put in semi-Fowler's position, given oxygen almost constantly for cyanosis, codein for restlessness and 3 minims of digifoline every three hours. A loud systolic murmur was heard at the apex and

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transmitted practically throughout the chest. Anteroposterior and lateral plates of the chest were taken which showed marked enlargement of the heart, incomplete aeration of the upper lobe on each side and slight tracheal contraction in the lateral projection, probably due to anteroposterior enlargement of the thymus. Examination of the blood showed R.B.C. 5,100,000, W.B.C. 12,900, hemoglobin 82 per cent. The urine examination on entrance was negative. The day following admission the child's temperature was 104 degrees F., and râles were heard over the left chest and axillary region. The child's condition became progressively worse. The temperature rose steadily and finally reached 108 degrees F. The respirations ceased forty-eight hours after admission. A clinical diagnosis of congenital heart disease with questionable bronchopneumonia was made.

Autopsy Findings.—An autopsy was done one and a half hours after death. The body, 60 cm. in length, appeared to be somewhat younger than the stated age. It was considerably undernourished and underweight. The lips and nail-beds showed a marked degree of cyanosis. There were no other external findings of significance.

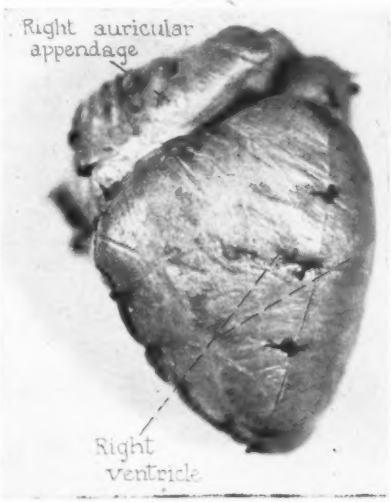

Fig. 1.—Shows the exterior of the heart. The anterior surface is made up entirely of right ventricle and auricle.

The autopsy was limited to the thorax only, but examination of the abdominal viscera while in situ revealed no abnormalities. The lower border of the liver measured 8 cm. below the ensiform cartilage and 5 cm. below the right costal margin. The diaphragm was beneath the sixth rib on the left and the fifth interspace on the right.

On removing the sternum, the enlarged heart was found to occupy a large portion of the thoracic cavity. Both lungs were compressed to the lateral thoracic wall, the left more so than the right. The thymus gland, occupying a small part of the anterior mediastinum, was normal in size.

The heart itself was markedly distended with blood. It lay almost transversely in the thoracic cavity. Fig. 1 shows the exterior of the heart as it lay in the mediastinum, with the anterior surface made up entirely of right ventricle and auricle. The heart was not measured while it was in the body, but after it was removed and had bled out, it measured $8 \times 6 \times 5.5$ cm. The apex was formed entirely by the right ventricle. The subepicardial fat was slightly decreased in amount. The musculature had the normal red color. There were no gross areas of fibrosis.

On opening the left side of the heart the ventricle was found to be very small. The wall averaged only 4 mm. in thickness. The inside diameter of the left ventricle measured only 1.5 × 2 cm. There were no interventricular openings. On opening the

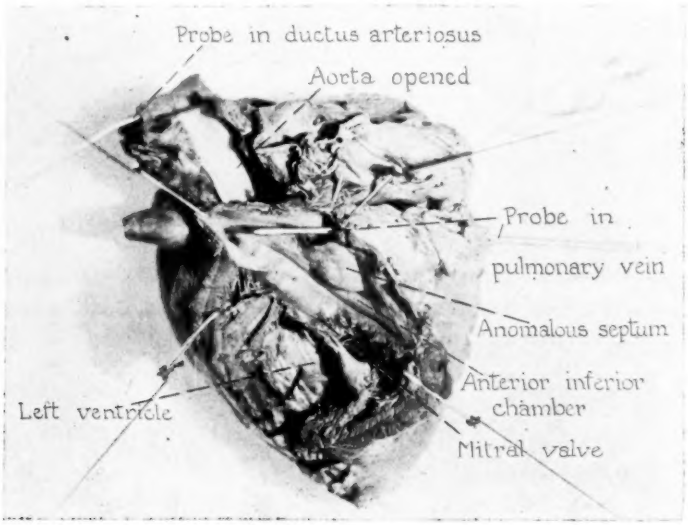

Fig. 2.—Shows the left heart opened. The probe is in the pulmonary vein and extends into the anteroinferior chamber of the left auricle. (The intraauricular opening has been stretched, causing it to appear much larger than it actually was.)

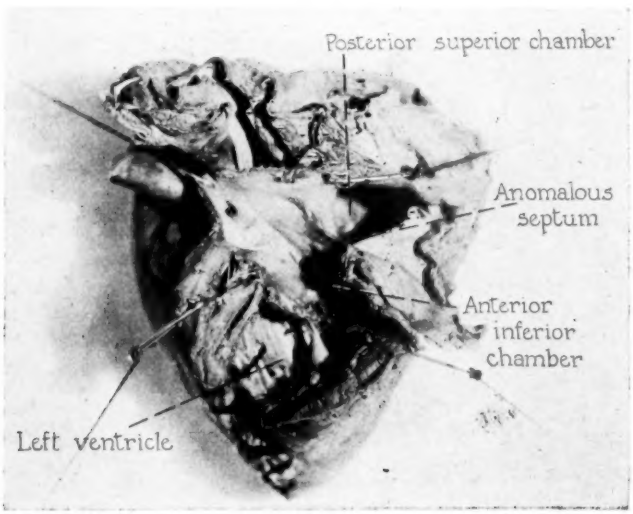

Fig. 3.—Same as Fig. 2 except that the anomalous septum has been put on the stretch, thereby showing the posterosuperior and anteroinferior chambers of the left auricle.

left auricle the mitral valve was found to be normal. Arising, however, from the posterolateral surface of the left auricle and extending toward the interauricular septum was an anomalous fibromuscular septum. This septum almost completely divided the left auricle into a larger posterosuperior, and a smaller anteroinferior

chamber, the inside diameters being 1.5 × 2.5 cm. and 1 × 1.5 cm. respectively. The septum measured 11 × 11 × 1 mm. Its free margin was adjacent to the interauricular septum, there being approximately only a 6 mm. slit for the blood to pass the septum (Fig. 2). The miniature auricular appendage was given off the anteroinferior chamber. Fig. 3 shows the left auricle and ventricle opened with anomalous septum.

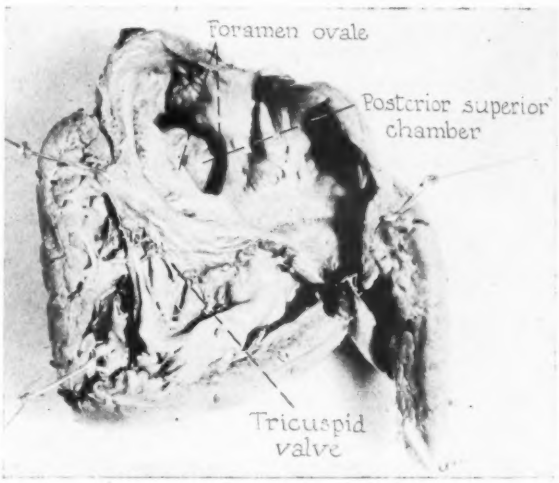

Fig. 4.—Interior of right heart showing the large foramen ovale and fusion of tricuspid valve. Note thickness of right ventricular wall.

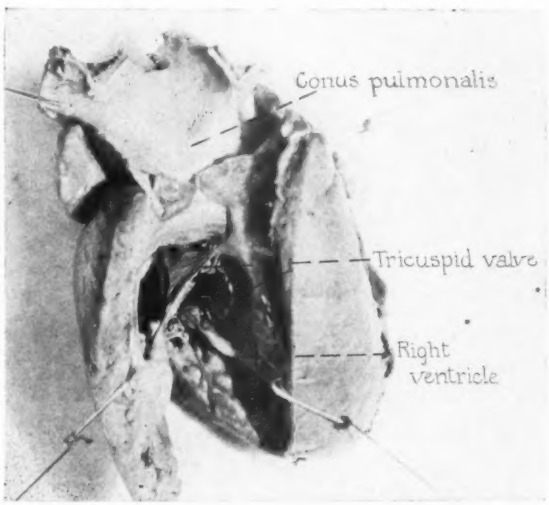

Fig. 5.—This picture shows the much dilated conus pulmonalis. (Compare with Fig. 2 which shows the aorta opened.)

The pulmonary veins had united and entered the posterosuperior chamber by a single vein. The much enlarged foramen ovale, measuring 1 × 2 cm., was located almost opposite the entrance of the pulmonary vein in the interauricular septum, thereby connecting the right auricle and the posterosuperior chamber.

The inside diameter of the right auricle measured 2.3 × 3 cm. Two of the cusps of the tricuspid valve were fused to produce in reality a bicuspid valve. The wall of the right ventricle averaged 8 mm. in thickness. The inside diameter of the cavity measured 4.3 × 4.5 cm. (Fig. 4.)

The pulmonary artery was considerably larger than the aorta, measuring 12 mm. in diameter, as compared with the aorta which measured 7.5 mm. in diameter (Fig. 5). The ductus arteriosus was patent, the lumen measuring 1.5 mm. in diameter. Although patent, it was evident that only a very small amount of blood was transmitted through it. The coronary vessels were normal in their distribution.

Microscopic Examination.—The aorta showed a patchy slight sclerosis of the intima. The cardiac musculature was well formed but rather hypertrophic for the age. The lungs showed partial atelectasis, congestion and small petechial hemorrhages. All of the vessels were dilated and their walls showed slight hypertrophy, particularly the arteries. There was no pneumonia. The peribronchial lymph nodes were rather hyperplastic. Both the larynx and esophagus were negative. The thymus showed fibroid rather than fatty atrophy. All adipose tissue showed starvation atrophy.

LITERATURE

There have been to date ten fully reported cases of this extremely interesting condition. The first case to be reported was by Church in 1868. Fowler in 1882 reported a case in which the patient lived forty-two years. He described a vertical membrane with many perforations. The presence of these perforations may be the significant factor in the relatively long length of life. Griffith reported two cases, the first in February, 1896, to the Anatomical Society, describing an upper and lower left auricle. The second, in 1903, was found in a man forty-three years old who died of Bright's disease. Sidney Martin in 1899 reported a case with upper and lower left auricle. Peter Potter and Ranson in 1904 reported a case found in a colored child who died of asphyxia. They described three right and two left pulmonary veins emptying into the upper posterior auricle. There were five small openings and one large opening in the anomalous septum. This case would tend to show that the presence of perforations in the septum is not a factor in determining the length of life. Borst reported a case found in a man thirty-eight years old. He described one left and four right pulmonary veins emptying into the upper posterior chamber. The foramen ovale was not patent. William and Abrikossoff, in 1906, reported a case found in an eleven-year-old boy. The left auricle was divided into two parts; the upper surface of the septum was concave, the lower convex. In the anteromedial part of the septum was a one-half centimeter opening. Peter Hosch in 1907 reported a case found in a twenty-five-day-old infant. There was a wide open ductus Botalli. Just posterior to the foramen ovale was another interauricular opening. Stoeber in 1908 reported a case with no opening in the anomalous septum of the left auricle. The veins of both upper lung lobes emptied into the right auricle, so only the veins of the lower lobes emptied into the upper small left auricle. The middle lobe of the right

lung was absent. There was a patent foramen ovale with a rudimentary valve, which was a continuation of the septum itself.

SUMMARY

There is no adequate embryological explanation for this anomalous septum in the left auricle, as there are no embryological rests from which it could develop. A plausible but not proved explanation is that the anomalous septum is an inversion or direct extension of the wall of the pulmonary vein, i.e., that in reality the smaller anteroinferior chamber is the normal left auricle, while the posterosuperior chamber is the dilated end of the pulmonary vein. Another possible explanation, although not applicable to this particular case, is that the anomalous septum may have arisen on the basis of (1) a fetal endocarditis or (2) an organization of thrombi.

This case had both a peripheral and aortic anoxemia. There was insufficient blood pumped from the left ventricle through the aorta to the peripheral circulation, and also this blood was mixed blood. The blood in the pulmonary circulation was sufficiently aerated, but the difficulty was that an insufficient amount of this blood reached the systemic circulation.

There are three factors which determine the duration of life in cases of this type: (1) the degree which the intraauricular septum prevents the blood from the pulmonary veins from passing through the mitral valve; (2) the size of the foramen ovale; (3) the relation of the intraauricular septum to the pulmonary veins and the foramen ovale.

The large foramen ovale was the only factor in this case which was conducive to long life. The fact that the anomalous septum so nearly completely divided the left auricle and thereby prevented the blood entering from the single pulmonary vein from passing the mitral valve to the left ventricle was a highly important factor in the short duration of life. Perhaps the most important factor, however, was the relation of the anomalous septum to the pulmonary veins and foramen ovale. The intraauricular septum in this case was very considerably stronger than the interauricular septum, and there was only a 6 mm. slit for the blood to pass the septum to reach the mitral valve and thus the left ventricle. The large foramen ovale was located almost opposite the entrance of the single pulmonary vein, thus making a much freer communication between the posterosuperior chamber of the left auricle with the right auricle, than with the anteroinferior chamber. These factors make it clear that the infant died a cardiac death with both an aortic and peripheral anoxemia.

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A QUALITATIVE COMPARISON OF VARIOUS DIGITALIS BODIES*

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TWO facts concerning the action of digitalis made possible the present investigation: (1) that digitalis acts upon a number of cardiac structures and produces a number of effects that can be detected in the electrocardiogram—sinus slowing, depression of conduction, increased rhythmicity of the A-V node or ventricle action upon the ventricle to change the T-wave or the R-T (or S-T) interval; and (2) that it requires more of the drug to produce some of these effects than others. This study was planned to ascertain whether or not the percentages of the fatal doses that produce the various changes are the same for different members of the digitalis group.

It is well known that digitalis leaves themselves, the pure glucosides and the various other members of the group, show wide differences in their chemical composition, physical properties, and pharmacological behavior (potency, rate of absorption, persistence of action, rapidity of onset of action). There have been no satisfactory studies of the question of qualitiative differences in the cardiac action of different digitalis bodies. Our use of the term, qualitative differences, may be best explained by the following illustration. Apomorphine may be prepared from morphine by the removal of a molecule of water, and each drug possesses most of the actions of the other, but the ratios of the intensity of action upon one structure to that upon another have been so markedly altered that in effect it amounts to a qualitative change in the actions of the drugs, so that one is used to stimulate the vomiting center and the other to depress the centers for the perception of pain. With reference to the digitalis bodies there was the question whether the chemical differences that render one less soluble in water, more readily absorbed from the gastrointestinal tract, more persistent in its action, may not also change the relative intensity of the different cardiac actions so that whereas, for example, ectopic beats with one specimen might be called forth only after 50 per cent of the fatal dose, these might be produced with another specimen after as little as 20 per cent of the fatal dose. Such differences would of course be qualitative in effect, because under such conditions, two specimens might be equally potent when measured in terms of the

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fatal action, yet one might be effective in slowing the sinus rate while the other would not, since in the latter case ectopic beats would appear before sufficient drug was present to slow the sinus. As a matter of fact, the results obtained by the usual methods of bio-assay of digitalis have been criticized on the ground that, although they furnish an estimate of the relative toxic activity of different specimens, we have not sufficient knowledge as to what extent these variations in toxic activity reflect the relative potency of different specimens with reference to phenomena occurring within the therapeutic range.

It was, therefore, an important question to determine, not only whether different members of the digitalis group produce the same types of cardiac changes, but whether the ratios of the amounts of the drug required to produce these changes to the amounts of the drug required to cause death are constant or vary for different digitalis bodies. This was made the subject of the present study. These data would afford an indication as to whether or not different digitalis bodies act with the same relative intensity (in relation to the fatal dose of that preparation) upon the different structures of the heart.

EXPERIMENTAL PROCEDURE

Seventy-seven experiments were carried out with six members of the digitalis group showing marked differences in their physical chemical and pharmacological properties:

1. A tincture of digitalis of an American grown leaf (of high potency).
2. A tincture of digitalis of a German grown leaf (of low potency).
3. A specimen of the chloroform fraction, "purified tincture"[1] of digitalis (well absorbed, very persistent in action).
4. A tincture of adonis (poorly absorbed, very persistent in action).
5. Ouabain (soluble in water, poorly absorbed, relatively brief persistence of action).
6. Digitoxin (Merck) (insoluble in water, well absorbed, very persistent in action).

The tinctures were diluted with 19 volumes of normal saline after the alcohol had been evaporated with moderate heat. A few of the experiments were carried out without the removal of the alcohol, but the results were essentially the same. The ouabain was dissolved in normal saline so as to make a solution of one in 100,000. The digitoxin was made into a one per cent alcoholic solution, and the latter was diluted with normal saline so as to make a solution of digitoxin of one in 10,000. About 5 per cent of the average fatal dose of the drug was injected from a burette at intervals of approximately five minutes until death. Cats were used in all. The animal was kept tied in the supine position throughout the experiment. Several electrocardiograms (only Lead II was used) at intervals of from five to fifteen minutes were taken before the injection of the drug was started. A tracing was then taken just before each injection. The movement of the string was sometimes observed throughout the experiment, and additional tracings were taken when abnormalities were detected. For each experiment there were approximately twenty-five separate tracings representing about 40 feet of electrocardiogram for analysis. Eleven to sixteen animals were used in the study of each preparation.

Anesthesia.—It was obviously desirable to carry out these experiments with the animals in a condition as nearly normal and constant as possible. It has been shown that ether anesthesia depresses the vagus and diminishes its response to stimulation by morphine.[2] Since some of the digitalis effects depend upon vagal influence, it seemed possible that the order of some of the changes resulting from the drug might be altered by the ether anesthesia. Furthermore, it appeared that a fixed anesthetic might in several ways prove more satisfactory. The effects of anesthesia by the intravenous injection of barbital sodium was tested in four animals. Each of three of these recieved 200 milligrams per kilogram in a single dose. When some anesthesia had been indueed, the injection of digitalis was carried out in the usual manner. The results were very variable, and while it cannot be stated whether larger numbers of experiments would not reveal a tendency different from that in unanesthetized animals, the behavior toward digitalis of each of these three is duplicated essentially in the unanesthetized group (see animals 14, 15, 16 of Table II). Electrocardiograms were taken approximately every fifteen minutes for several control records before the barbital, then after the barbital injections for periods of 165 minutes (in one experiment in which only barbital was used), 272 minutes (animal 14 of Table II), 233 minutes (animal 15 of Table II), and 141 minutes (animal 16 of Table II). In the first animal the heart rate varied between 140 and 160 a minute during forty minutes of control. During the first ten minutes following the injection of 150 milligrams per kilogram there was almost incessant struggling. An additional 100 milligrams per kilogram were injected, and after about twenty minutes the animal became quiet. The heart rate, however, was accelerated to 220 a minute which rate gradually diminished during the next two hours to 180 a minute. The mean blood pressure (taken with the mercury manometer from the carotid artery) had fallen from 180 to 126 mm. The form of the electrocardiographic deflections showed no significant changes. The temperature fell to 99.4 degrees F. and the animal began to shiver. The condition of the animal was, therefore, not constant for any considerable period after the injection. In experiment 14 (Table II) the heart rate diminished gradually from 225 to 150 during a period of two and one-half hours, and the blood pressure fell from 160 to 100 mm. In experiment 15 (Table II) the rate at first increased from 210 to 255 a minute, then gradually diminished during a period of about four hours to 185 a minute with reduction of the blood pressure during this time to 98 mm. The heart rate, however, continued to fall during the digitalis injection, and it was not possible to ascertain whether that was due to the digitalis or merely a continuation of the barbital action. In experiment 16 (Table II) the heart rate remained practically constant, though the animal continued to be restless throughout the experiment. The use of the fixed anesthetic was discontinued because the reaction to the barbital varied greatly; there was considerable restlessness even after very large doses, and there were progressive changes in the heart rate and blood pressure as well as in the general condition of the animal which occurred gradually over long periods of time.

The operation for the insertion of the cannula into the saphenous vein was performed during local anesthesia with phenol in oil, and the injections were made without any general anesthesia. Occasionally a cat tied down on its back lies there very quietly, but often there is repeated struggling resulting in wide fluctuations in the heart rate, and sometimes changes in the electrical axis of the heart altering the direction of the deflections, such as inversion of the T-wave, or change of an R to an S-wave. These changes were usually temporary and disappeared in subsequent tracings. We also found that ectopic beats were produced by struggling after doses of digitalis which were insufficient to produce them when the animal was quiet. Such response would be expected in view of the fact that some of the changes produced by digitalis depended upon the activity of the extracardial nerves,

and the changes will appear with smaller or larger doses depending upon whether struggling has intensified or diminished the activity of these nerves. This has been made the subject of a separate investigation. In dispensing with the anesthesia we have obviated the necessity of considering possible disturbing factors of another drug. It is well to note, however, that the condition of the unanesthetized animal is not normal in the strict sense and far from constant; the results obtained with digitalis in the animal whose ventricle is subjected to strong accelerator stimuli (as in violent struggle) are not the same in some respects as those obtained when the latter stimuli are absent. The data obtained under the conditions of these experiments, however, serve sufficiently to compare the behavior of different members of this group of drugs.

Electrocardiographic Criteria.—The effect of the drugs upon the sinus rate has not been considered in the interpretation of the results. With each of the specimens there were some instances in which the heart rate was greatly slowed during the injections. It was not possible, however, to ascertain the doses producing the first changes because of the marked fluctuations of the rates in the controls. The percentage of the fatal dose which produced the greatest slowing is indicated in the tables; in some instances no percentage is given (dashes in the tables) because while the slowest rate during the injection was actually slower than that during the control, the fluctuations were so wide that it was deemed unsafe to assume that the slowing was due to the drug.

The P-R intervals were determined by taking an average of about ten readings in each tracing (from beginning of P to beginning of Q or R). The change in conduction was relatively fixed for successive beats in most tracings; occasionally, however, it was of the type in which successive beats showed progressively increasing P-R intervals until dropped beats occurred (for example, animal 10 of Table VI). It is probable that the prolonged conduction in most instances was due to direct depression of the conducting system rather than to vagal influence or as the result of sinus slowing, because the vagus tone in most instances was very low as seen from the rapid heart rates, the first changes in conduction frequently occurred without any change in the sinus rate, and because when a change in conduction occurred it was usually persistent and not abolished by struggling which inhibited the vagus. The prolongation of conduction from tracing to tracing often occurred with almost imperceptible gradations; hence it was difficult to ascertain the first change. Since the average of several intervals in each of several control tracings usually showed variations in conduction time of less than 0.05 second, a tracing was regarded as showing a prolonged P-R interval only when a change of 0.05 second or more was present.

The changes produced in the T-wave and the R-T (S-T) segment were extremely variable. The form of the changes varied with the

form of the control deflections. The most constant feature was that a positive deflection became isoelectric, and then negative. The form of the R-T segment (or S-T segment when the S-wave was present) was found to be much more constant than the T-wave and therefore more satisfactory to follow as an index of digitalis action. The T-wave was extremely variable showing forms that were isoelectric, high, low, and occasionally negative in successive tracings of the control period, or even in the same tracing. Illustrations of the different types of changes in the T-wave, R-T and S-T segments will be published in another communication. As was the case with the P-R intervals, the changes sometimes occurred very gradually and with the marked variations in the controls; it was difficult to determine with precision in which tracings the first changes due to the drug had occurred. In the tables we refer to the dose of the drug producing the first change in the RT-T period. In some instances this represents the first definite change in the T-wave, in some, that of the R-T (S-T) segment, and in others, it represents a simultaneous change in both, depending upon which showed the first unmistakable deviation from the control tracings.

The ectopic beats were of either nodal or ventricular origin. At times they appeared as isolated beats or a begeminal rhythm (every other beat a ventricular premature contraction); they often appeared for the first time as a ventricular tachycardia. In some animals ectopic beats occurred in one tracing, then were absent in the next two or three tracings even though additional doses of the drug had been injected. The early appearance of ectopic beats was often due to struggling, a phenomenon to which we have already referred. In three animals of the series ventricular ectopic beats appeared after a struggle before the injection of the drug was started. Even though these animals were apparently susceptible to spontaneous ectopic beats, they required practically the same dose of the drug to induce them as did normal animals. This is in harmony with the observation that patients susceptible to spontaneous premature contractions do not necessarily show any special susceptibility to their production by the digitalis bodies.[3]

Ventricular fibrillation was the cause of death in every animal used in this study.

RESULTS

The detailed analyses of the electrocardiograms are tabulated in the Tables I to VI. They show the extent of some of the changes as well as the doses required to produce them. These data are necessary to convey the proper appreciation of the extreme variability in the behavior of different animals to the *same preparation*. For example, animals 2 and 4 (Table II) required the same fatal dose, but in the first the only electrocardiographic change was an ectopic rhythm after

TABLE I

TINCTURE DIGITALIS (AMERICAN LEAF)*

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	C.C. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	C.C. PER KG.	% OF FATAL DOSE	C.C. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	C.C. PER KG.	% OF FATAL DOSE
1	2.60	0.26	280	260	0.070	----	----	0.10	37	---	--	--	--	0.19	75
2	2.74	0.31	180	205	0.090	0.11	----	---	--	0.15	49	--	--	0.18	57
3	2.60	0.33	220	210	0.080	----	-- -	0.10	30	---	--	--	--	0.16	50
4	2.22	0.34	210	220	0.070	0.080	0.100	0.09	27	0.16	47	53	--	0.18	53
5	2.30	0.35	200	160	0.078	0.085	----	0.10	30	0.10	30	--	30	0.10	30
6	2.92	0.36	175	180	0.070	0.080	----	0.12	33	0.22	60	--	--	0.14	40
7	2.24	0.38	225	160	0.075	0.085	0.120	0.09	24	0.11	30	47	35	0.13	35
8	2.40	0.44	220	135	0.070	0.080	0.095	0.13	29	0.31	71	76	71	0.27	61
9	2.50	0.45	210	180	0.070	0.080	----	0.13	29	0.26	57	--	--	0.16	36
10	2.62	0.46	305	250	0.070	0.075	----	0.14	30	0.18	40	--	45	0.21	45
11	3.30	0.56	220	190	0.060	0.080	0.100	0.15	27	0.27	49	57	--	0.24	42
12	2.00	0.56	165	95	0.080	0.080	0.12-0.16	---	--	0.21	38	56	56	0.31	56

*From evidence subsequently obtained it appears that the leaf was not as active as indicated by these figures but that the preparation was probably more than a 10 per cent tincture.

TABLE II

TINCTURE DIGITALIS (GERMAN LEAF)

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	MG. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	MG. PER KG.	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE
1	2.36	100	190	165	0.077	0.085	0.091	64	64	42	42	64	64	64	64
2	2.70	111	150	160	0.070	----	----	--	--	--	--	--	--	33	30
3	1.68	111	260	200	0.068	----	----	41	37	--	--	--	47	58	52
4	3.06	111	180	140	0.077	0.085	0.110	38	34	45	41	68	55	72	65
5	2.00	115	230	180	0.068	0.075	0.100	30	26	70	61	74	62	70	61
6	1.92	120	140	160	0.085	----	----	37	30	--	--	--	--	37	30
7	3.86	120	190	210	0.073	0.080	----	--	--	41	34	--	--	53	44
8	2.70	122	165	130	0.080	0.091	0.110	36	30	59	48	73	66	59	48
9	2.32	131	180	180	0.075	----	----	45	34	--	--	--	--	45	34
10	2.00	135	220	160	0.079	0.093	0.105	30	22	81	60	69	54	93	69
11	2.18	137	140	150	0.075	0.080	0.088	41	30	55	40	63	--	73	53
12	2.60	150	220	210	0.080	0.090	0.12-0.20	40	27	75	50	58	--	64	43
13	1.52	151	220	250	0.074	0.080	0.110	26	17	92	61	74	--	98	65
14	2.72	72	140	140	0.080	----	----	--	--	--	--	--	--	21	29
15	2.42	111	185	150	0.072	0.080	0.115	41	37	70	63	82	28	99	89
16	1.96	123	190	180	0.060	----	----	41	33	--	--	--	--	51	42

TABLE III

CHLOROFORM FRACTION ("PURIFIED TINCTURE")

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	C.C. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	C.C. PER KG.	% OF FATAL DOSE	C.C. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	C.C. PER KG.	% OF FATAL DOSE
1	2.98	0.65	245	225	0.080	----	----	0.15	23	----	--	--	--	0.35	54
2	2.06	0.68	220	190	0.080	----	----	----	--	----	--	--	--	0.15	22
3	2.18	0.69	190	150	0.068	0.078	----	0.14	20	0.28	40	--	40	0.23	33
4	1.96	0.71	240	160	0.068	0.075	----	0.25	36	0.36	50	--	50	0.36	50
5	3.40	0.90	210	170	0.070	----	----	0.18	20	----	--	--	--	0.25	28
6	2.06	0.92	190	150	0.078	0.090	0.095	0.34	37	0.48	53	63	58	0.63	68
7	1.76	0.95	220	190	0.060	----	----	0.31	32	----	--	--	--	0.67	70
8	2.80	0.96	230	155	0.065	0.075	0.095	0.21	22	0.43	44	56	56	0.48	50
9	1.42	1.00	210	190	0.078	0.090	----	0.24	24	0.48	48	--	--	0.62	62
10	2.56	1.00	210	172	0.070	0.075	----	0.24	24	0.29	30	35	--	0.35	35
11	1.94	1.43	190	140	0.075	0.090	0.100	0.32	23	0.55	39	55	39	0.97	68

TABLE IV

TINCTURE ADONIS

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	MG. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	MG. PER KG.	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE
1	2.80	125	170	150	0.080	0.085	----	--	--	36	29	--	--	36	29
2	2.34	134	180	180	0.085	0.090	0.100	44	33	60	45	44	--	59	44
3	3.44	142	235	195	0.070	0.080	0.095	46	33	64	45	55	55	78	55
4	2.72	147	260	210	0.075	----	----	--	--	--	--	--	37	73	50
5	2.20	150	168	150	0.080	----	----	41	31	--	--	--	--	93	62
6	2.62	152	175	185	0.068	0.080	----	--	--	61	40	--	--	91	60
7	2.20	152	250	215	0.075	0.080	0.085	41	31	64	42	52	--	94	62
8	2.50	152	210	205	0.065	----	----	41	31	--	--	--	--	96	63
9	3.46	156	230	140	0.078	0.085	0.100	59	38	61	39	46	46	48	31
10	4.10	161	150	120	0.090	0.110	----	24	15	74	46	--	45	103	64
11	3.66	169	185	140	0.075	----	----	59	35	--	--	--	62	119	70
12	2.42	175	200	145	0.080	----	----	72	41	--	--	--	57	119	68
13	2.78	201	225	195	0.070	0.080	0.120	48	24	80	40	48	--	80	40

TABLE V

OUABAIN*

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	MG. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	MG. PER KG.	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE
1	1.78	0.075	180	240	0.069	----	----	0.014	19	----	--	--	--	0.053	71
2	1.42	0.120	195	180	0.068	----	----	0.028	24	----	--	--	--	0.050	41
3	2.62	0.124	180	120	0.080	0.087	----	0.054	43	0.070	54	--	60	0.080	64
4	1.50	0.126	160	175	0.080	0.085	----	0.013	11	0.066	53	--	--	0.093	74
5	2.64	0.132	190	110	0.074	0.079	0.085	0.040	30	0.054	40	55	55	0.086	65
6	2.44	0.135	200	190	0.073	0.080	0.090	0.045	33	0.069	51	66	--	0.089	66
7	1.84	0.138	210	170	0.070	0.075	----	----	--	0.079	58	--	--	0.092	67
8	1.74	0.139	160	100	0.065	0.070	0.085	0.071	51	0.077	56	66	66	0.064	46
9	2.24	0.143	240	140	0.069	0.075	0.120	0.072	50	0.085	60	70	70	0.100	70
10	1.84	0.146	220	180	0.080	----	----	0.038	26	----	--	--	--	0.065	44
11	2.60	0.155	200	120	0.070	----	----	0.077	49	----	--	--	56	0.091	59
12	2.42	0.186	230	200	0.070	0.075	----	0.051	27	0.076	41	--	--	0.116	63

*This specimen of ouabain was slightly yellowish, and as also indicated by the fatal dose it was probably not pure.

TABLE VI

DIGITOXIN (MERCK)

NO.	WEIGHT OF ANIMAL	FATAL DOSE	SLOWEST SINUS RATE		LONGEST P-R IN CONTROL	FIRST INCREASED P-R	LONGEST P-R IN PERIOD OF INJECTION	MINIMUM DOSE OF DRUG THAT PRODUCED:							
								CHANGE IN RT-T		FIRST INCREASED P-R		LONGEST P-R	SLOWEST SINUS RATE	ECTOPIC BEATS	
	KG.	MG. PER KG.	IN CONTROL	IN PERIOD OF INJECTION	SEC.	SEC.	SEC.	MG. PER KG.	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE	% OF FATAL DOSE	% OF FATAL DOSE	MG. PER KG.	% OF FATAL DOSE
1	3.20	0.19	190	240	0.070	0.080	-- --	0.03	17	0.11	57	--	--	0.10	50
2	2.52	0.26	235	230	0.070	0.078	0.090	0.16	62	0.12	46	62	--	0.26	100
3	1.92	0.34	260	260	0.070	-- --	----	0.16	46	----	--	--	--	0.26	67
4	2.34	0.36	240	190	0 070	0.080	----	-- --	--	0 22	60	--	60	0 23	65
5	3.46	0.38	160	270	0.080	0.12-0.18	----	0.06	16	0.20	53	--	--	0.24	62
6	3.12	0.38	190	160	0 080	----	----	0.07	18	----	--	--	60	0.18	47
7	3.30	0.39	255	250	0.079	0.085	----	0.15	38	0.24	62	--	--	0.23	59
8	2.62	0.40	225	230	0.075	----	----	0.13	33	----	--	--	--	0.29	72
9	2.88	0.41	200	190	0.065	----	----	----	--	----	--	--	--	0.17	41
10	2.00	0.43	190	175	0.065	----	----	-- --	--	----	--	--	--	0.23	53
11	2.86	0.44	200	200	0.080	----	----	0.15	34	.	--	--	--	0.27	62
12	2.88	0.45	185	180	0.075	0.085	----	0.17	37	0.27	59	--	--	0.32	69
13	2.00	0.47	240	240	0.075	0.100	----	0.15	32	0.27	58	--	--	0.30	64

30 per cent of the fatal dose, while in the second a T-wave change appeared after 34 per cent, P-R lengthening after 41 per cent, and ectopic beats not until 65 per cent of the fatal dose had been injected. Animals 1 and 12 (Table II) each required 64 milligrams per kilogram to call forth ectopic beats, but the first required only 100 milligrams to cause death while the second required 150 milligrams. With the same preparations, doses that may serve merely to produce ectopic beats in some animals (animals 7 and 11 of Table III) may be sufficient to cause death in others (animals 1 to 8 of Table III). The appearance of ectopic beats may indicate a high degree of digitalis poisoning in some animals (89 per cent of the fatal dose in animal 15 of Table II), while in others, it may indicate a very early stage of digitalis action (29 per cent of the fatal dose in animal 14 of Table II). In the order in which the experiments of Table II were carried out it was a rather striking accident that five of the first seven figures for the production of ectopic beats were below 50 per cent whereas six of the following nine figures were above 50 per cent of the fatal dose.

TABLE VII

COMPARING DIFFERENT DIGITALIS BODIES WITH REFERENCE TO THE AVERAGE PERCENTAGE OF THE FATAL DOSE PRODUCING THE FIRST CHANGE IN VARIOUS ELECTROCARDIOGRAPHIC SIGNS

SPECIMEN OF DRUG	CHANGE IN RT-T	FIRST INCREASED P-R	ECTOPIC BEATS
Tr. Dig. (American)	30 (24-37)	47 (30-71)	48 (30- 75)
Tr. Dig. (German)	32 (17-64)	50 (34-63)	51 (29- 89)
Chloroform Fraction	26 (20-37)	43 (30-53)	49 (22- 70)
Tr. Adonis	31 (15-41)	41 (29-46)	54 (29- 70)
Ouabain	33 (11-51)	52 (40-60)	61 (41- 74)
Digitoxin	33 (16-62)	56 (46-60)	62 (41-100)
Average	31	48	54

The important data are summarized in Table VII. This shows the average percentage of the fatal dose of each of the preparations required to produce the first change in the RT-T, the first prolongation of the P-R interval, and ectopic beats. It is evident that each of these three phenomena is called forth by a percentage of the fatal dose that is the same for these six widely different members of the digitalis group. The figures (in parenthesis) showing the wide range of individual variations make it possible to understand better why no significance can be attached to the minor differences in the averages for the different preparations; namely, 26 to 33 per cent for the RT-T change, 41 to 56 per cent for the first increased P-R, and 48 to 62 per cent for the ectopic beat.

These results could be assumed to indicate directly the relative intensity of action of the digitalis bodies upon different cardiac structures only if each electrocardiographic sign represented an action

upon a single structure. The T-wave change produced by digitalis is probably due to a direct action upon the ventricle.[4] We have already called attention to the facts that indicate that the prolongation of conduction time under the condition of our experiments was due in most instances to a peripheral depression of the A-V conducting system. In the case of the ectopic beats it was necessary to consider several structures. To illustrate, theoretically two specimens of the drug might produce ectopic beats with similar percentages of the fatal dose, yet the seat of action might be upon entirely different structures, because ectopic beats may be called forth by directly increasing the rhythmicity of the ventricle (or A-V node), by stimulation of the accelerator nerves, by suppression of the sinus through vagus stimulation, by the production of an A-V block, or by various combinations of these factors. As a matter of fact, the digitalis bodies do produce them in unanesthetized cats usually through a combination of these factors, the most important of which appears to be a direct action upon the ventricle (or A-V node) to increase its rhythmicity, and no essential differences in this respect were detected with different members of the digitalis group as shown in another study.[5] It is safe to say, therefore, that as far as these experiments go, they indicate that different digitalis bodies act with essentially the same relative intensity (in relation to the fatal dose) upon different cardiac structures.

Robinson and Wilson[6] found that approximately 25 per cent of a fatal dose of digitalis produced the first change in the T-wave, 50 per cent produced a definite change in the P-R interval and about 75 per cent called forth ectopic beats. In Table VII it is seen that our average for the T-wave change corresponds to theirs, but the other two phenomena occur with practically the same percentage of the fatal dose, namely, 48 and 54 per cent, instead of 50 and 75 per cent of the fatal dose as in their experiments. The figures in Tables I to VI that bear upon the relationship between the dosage required for the first prolongation of conduction and the production of ectopic beats have been further analyzed and the results summarized in Table VIII. It shows that in approximately one-half of the cases, conduction became prolonged before ectopic beats appeared, and in the other half the conditions were just reversed. Occasionally both phenomena were seen for the first time in the same tracing. When the increased P-R interval occurred first, it usually required from about 5 to 25 per cent of the fatal dose of additional drug to produce ectopic beats. When the ectopic rhythm occurred first, it was usually not possible to determine the conduction time except in occasional instances in which the abnormal rhythm was interrupted by a regular sinus rhythm in the tracing. It is probable that the lower average for the production of ectopic beats in our ex-

periments than in those of Robinson and Wilson is due, as we have shown in another study,[5] to the fact that their animals were anesthetized with ether.

TABLE VIII

SPECIMEN OF DRUG	NUMBER OF CASES IN WHICH		
	P-R CHANGE OCCURRED FIRST	ECTOPIC BEATS OCCURRED FIRST	BOTH OCCURRED FOR FIRST TIME IN SAME RECORD
Tr. Dig. (American)	5	6	1
Tr. Dig. (German)	7	7	2
Chloroform Fraction	5	5	1
Tr. Adonis	5	6	2
Ouabain	5	7	0
Digitoxin	5	8	0

DISCUSSION

A stock argument found in commercial advertisements runs, "If digitalis is ineffective or badly tolerated" use this or that digitalis specialty. There are many papers in the literature indicating qualitative differences in the cardiac action of different digitalis bodies. In not a single case are the statements supported by satisfactory evidence. For example, Yamanouchi[7] stated that strophanthus was three times as effective as digitalis (in proportion to the fatal dose) in causing cardiac slowing in the cat under ether anesthesia. An examination of his table shows that he obtained cardiac slowing after from 3 to 7 per cent of the fatal dose of his preparation of strophanthus. There is no statement as to the amount of slowing; and in view of the variability of the cat's heart rate during ether anesthesia, the depression of the vagus by ether, and the well-known fact that any considerable slowing of the cat's heart occurs only after more nearly 50 per cent of a fatal dose of digitalis, one can attach no significance to the results of such experiments.

Vaquez[8] in the latest edition of his textbook (1924) stated that he found the margin of safety between the effective and toxic dose smaller for amorphous strophanthin than for ouabain (Arnaud), that both of these substances augment the "tonus" without acting upon the other functions of the myocardium, that he has never detected changes in conductivity or excitability, and that extrasystoles, so frequent after digitalis, are exceptional after these drugs. From his statements regarding dosage as well as from his conclusions regarding the mode of action of ouabain, it is apparent that Vaquez had used far too small doses of the drug, and that as far as indicating any qualitative differences in the cardiac actions of amorphous strophanthin, ouabain, and digitalis, it is hardly necessary to say that his views are wholly incorrect. One needs only to give a suitable dose of ouabain to a patient with auricular fibrillation and a rapid ventricular rate[9] to

appreciate that ouabain does depress conduction in a very striking manner, or to give a suitable dose to an animal to see that the production of ectopic beats, so far from being rare, is impossible to avoid.

Langley[10] used seven preparations of digitalis of different potencies in patients with auricular fibrillation. He attempted to correlate the degree of ventricular slowing and the production of vomiting with the biological potency of the drug. On the basis of the behavior of two or three patients in small groups after doses that were not comparable in activity he allowed himself to infer that the substance causing cardiac slowing is not identical with that producing the toxic effect (vomiting), that the toxic substance may be responsible for a high potency reading by biological assay while the drug may in fact be of low therapeutic value, that vomiting may result from this toxic factor before adequate therapeutic effects have occurred. The suggestion that the therapeutic action of digitalis is due to one substance and the toxic action (vomiting) to another, cannot be considered seriously in view of the fact that pure digitalis bodies like ouabain and digitoxin possess not only the therapeutic but the emetic action. It is of course conceivable that a preparation may be very active by intravenous injection in a bio-assay, and yet prove to be of low potency when given by oral administration to man because of a poorly absorbable fraction. Actually such conditions are exceedingly uncommon. Langley presents no satisfactory evidence to support his statement that some preparations of digitalis are so actively emetic that vomiting is produced before sufficient drug is present to produce the therapeutic effects. It would be necessary to show with suitable controls that other preparations would produce the therapeutic effects without emesis in the same patients. The question that has been raised, however, involves a matter of very great practical importance because it is not difficult to find clinical cases which on the surface seem to indicate that the emetic action of a specimen of the drug is preventing effective digitalization. For example, digitalis often fails to check the progress of failure in the terminal stage of heart disease.[3] If the drug is continued or administered in larger doses in an effort to relieve symptoms, toxic effects are often induced though no therapeutic effects are in evidence. It is clear that the drug is not at fault in such cases.

Hatcher and Eggleston[11] have shown that the relative emetic activity of the various members of the digitalis group shows considerable differences when the drug is given intravenously in animals. Thus true digitalin caused vomiting with an average of 22 per cent of the fatal dose, while the average for the specimen of digitalis they employed was 46 per cent of the fatal. There is no evidence at present as to whether different specimens of digitalis itself show differences in their relative emetic activity.

The observations that one preparation of digitalis has produced more satisfactory therapeutic results or less toxic effects than another require very close scrutiny because there are many factors which if left out of consideration may lead to erroneous conclusions. In a few instances in which one of us (H. G.) has had an opportunity to examine in detail or to check the evidence for such statements there has usually appeared to be some factor not inherent in the drug. Improper dosage seems to be the most common source of error; preparations are assumed to show differences in their cardiac actions when they have not been used in strictly comparable doses in terms of effects upon patients. In one case a patient was digitalized fully (to the point of minor toxic symptoms) by a tincture of digitalis, and there was little or no improvement in the symptoms of congestive heart failure. After a period of about two weeks the patient was fully digitalized by a proprietary preparation, and marked improvement resulted. This was interpreted by the physician as an indication that the one preparation had a greater relative therapeutic activity than the other. Yet it is not uncommon that a patient fails to improve appreciably after the first course of digitalization but shows striking improvement after a second course a week or two later with the *same preparation.* This can be demonstrated in patients after a period of control in bed without medication, during which time a constant level in the general condition has been reached (water intake and output, body weight, heart rate, symptoms).

The three specimens of digitalis, "A," "B," and "C," submitted by Professor Magnus for the Hygiene Committee of the League of Nations, were tested in various clinics and laboratories. A clinical study of these specimens on a relatively small group of patients was reported by Martin[12] of Baltimore and on a larger group by Gilchrist and Lyon[13] of Edinburgh. Martin found that the therapeutic effects appeared before any symptoms or signs of digitalis intoxication in practically every case, while Gilchrist and Lyon were troubled by the occurrence of nausea and vomiting especially with specimens "B" and "C" before one-half of the total dose had been administered which they attributed to a local irritant action. In both studies the powdered leaf was employed in large doses. Martin's patients received the drug in small capsules of 0.2 gram each, while those of Gilchrist and Lyon received bulky cachets which they state some patients had difficulty in swallowing. This may have been a factor in producing the nausea and vomiting. Sufficient data are not given for a more precise comparison of the technic of administration. In any event, that specimens "B" and "C" were more irritant to the stomachs of Englishmen than to those of Americans is much less likely than the assumption that nausea and vomiting were due to some factor other than the direct irritation of the stomach by the drug.

Two commercial specimens were employed in a study of digitalis in pneumonia.[14] When comparable doses of the two specimens were given in terms of their supposed potency, about one-half of the patients vomited after one of the specimens and very few vomited after the other. This suggested that one specimen was more actively emetic than the other in relation to the fatal dose for animals. When the two were tested it was found that the one which caused the vomiting had been incorrectly labelled by the manufacturer and that therefore the vomiting was not due to a greater relative emetic activity but that the patients had really received about twice as much digitalis as was indicated in terms of activity. These instances are cited merely to call attention to the numerous factors that may give rise to apparent differences in the action of various specimens of digitalis and the dangers attending the interpretation of observations that appear to indicate essential differences in the cardiac action of different members of the digitalis group.

In the present study we have not examined all the actions of the digitalis bodies, not even the most important one, namely, that action directly upon the heart which improves myocardial efficiency in congestive heart failure (the improvement may be the result of a number of direct and indirect actions). We have, however, compared a number of cardiac actions within both the therapeutic and toxic range of widely different digitalis bodies, and the results show that these act with the same relative intensity upon different cardiac structures. A critical appraisal of any data purporting to show essential qualitative differences between digitalis bodies must not fail to take cognizance of the extreme variability of the reaction of *different individuals* toward the *same preparation* injected in the same way. As we have already shown the law of chance under these conditions sometimes juggles the data in such a way as to make it difficult indeed to escape erroneous conclusions.

SUMMARY

In the present study seventy-seven experiments were carried out with six widely different members of the digitalis group in order to ascertain whether these showed any qualitative differences in the cardiac action. Electrocardiographic criteria of digitalis action were used, and the relative intensity of action upon different cardiac structures (in relation to the fatal dose) was used to indicate qualitative differences.

The results show that widely different digitalis bodies have the same qualitative cardiac actions but that there are extraordinary individual differences in response to the same preparation. This fact may be an important factor in the confusion found in the clinical literature.

There are numerous references in the literature to qualitative dif-

ferences in the cardiac action of different members of the digitalis group, and implications that such differences exist are common in commercial advertisements, but in no single instance are these statements substantiated by adequately controlled experiments.

Examples are cited showing some of the sources of error in the interpretation of observations which appear to indicate qualitative differences in the cardiac action of different digitalis bodies.

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THE HEART IN THROMBO-ANGIITIS OBLITERANS*

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WITH more intensive study of thrombo-angiitis obliterans, evidence is accumulating which points to the fact that this disease is not always limited to the peripheral blood vessels. It is becoming increasingly evident that there may be simultaneous involvement of arteries in other parts of the body. The occasional complaint of anginal symptoms in some of our patients suffering from thrombo-angiitis suggested to us the systematic study of a series of fifty consecutive cases of this disease in order to determine the incidence of cardiac lesions.

In this research we have avoided, as far as possible, the inclusion of cases of peripheral atherosclerosis. In some instances the differential diagnosis between atherosclerosis and thrombo-angiitis obliterans has been difficult, but wherever any doubt as to classification arose, the case was not included in this series. The simultaneous occurrence of peripheral atherosclerosis with coronary artery sclerosis is a well-established fact and will not be discussed in this communication. The possibility of atherosclerosis superimposed upon thrombo-angiitis obliterans must also be considered in the case of older individuals.

The patients comprising this group were, for the most part, young males. In every case the onset of symptoms in the extremities was prior to the age of 45 years. Every patient presented conclusive evidence of peripheral arterial disease, which, as far as our present knowledge goes, we believe to be thrombo-angiitis.

Each patient had been a heavy cigarette smoker for a number of years. Nine of these fifty cases (eighteen per cent) had had superficial migrating phlebitis of the extremities at some time during the course of the illness. Of these nine cases, two were in the group with cardiac lesions. In no instance was there a history of lues, nor was the Wassermann reaction positive in any case.

While we have been concerned, primarily, with the detection of involvement of the coronary arteries in the disease process known as thrombo-angiitis obliterans, the difficulty of establishing this fact by clinical study alone has been constantly recognized. The ultimate diagnosis of thrombo-angiitis obliterans from the pathological standpoint rests upon the discovery of the typical inflammatory lesion in the blood vessels, which, in the case of coronary arteries can be obtained only at autopsy. Clinically, the diagnosis of coronary artery disease is justified when electrocardiographic study reveals certain changes

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from the normal. These changes are assumed to be the result of disturbances of the myocardium and conduction system of the heart produced by interference with blood supply from the coronary arteries.

The cardiac status of each patient was investigated under the following headings: (1) Subjective cardiac symptoms. (2) Physical examination of the heart. (3) X-ray examination of the heart. (4) Electrocardiography.

The subjective symptoms of coronary artery disease were considered from the standpoint of the symptom-complex known as angina pectoris in its various manifestations, such as precordial pain, substernal distress, choking or constricting dyspnea. As pointed out by Libman, dyspnea on exertion may be complained of, and not pain. If, however, the patient is not very hyposensitive, he may feel pain. Further evidence of myocardial damage was sought in the physical examination. The character of the apical impulse was observed. Cardiac outlines were noted, although enlargement of the heart borders has been found to have no specific value in the determination of coronary disease. Feeble heart sounds were considered suggestive of myocardial change. Gallop rhythm is of importance as a diagnostic sign. Murmurs were considered of no confirmatory value in determining the presence of myocardial or coronary disease. Bilateral blood pressure readings were made. Teleroentgenograms were used to detect abnormalities of the cardiac outlines.

In this study, the greatest stress was placed upon the electrocardiogram. Due cognizance was taken of the fact that rheumatic fever may be responsible for almost any type of electrocardiographic change, but since none of our cases have at any time manifested this disease, we feel that this factor may be disregarded in the present study.

The accepted changes in the electrocardiogram indicative of myocardial change are the following:

(1) Intra-ventricular conduction defects as described by Oppenheimer and Rothschild. These include prolongation of the QRS interval and distortion of QRS complexes which must be observed in several examinations.

(2) Changes in the T-wave. Negative T-waves in more than one lead are suggestive. According to Pardee, the cove plane T-wave is definite evidence of coronary involvement.

(3) Arrhythmias, while not specific, were considered in the final determination of whether or not myocardial damage was present.

Of the fifty cases studied, five showed definite evidence of myocardial disturbance which we attributed to a probable underlying coronary artery disease. Of the remaining forty-five cases, thirty did not present sufficient evidence. While fifteen cases were entirely negative, it must not be forgotten that coronary disease may be present without yielding any clinical or electrocardiographic manifestation.

A synopsis of the records of the five patients showing evidence of myocardial damage follows:

CASE REPORTS

A. S.—Case No. 20. The patient was a Russian Jew, 52 years old. At the age of 38 years he developed an ulcer of the left foot. This lesion apparently marked the onset of thrombo-angiitis obliterans. Twelve years later the left leg was amputated because of extensive gangrene. Subsequently the patient developed typical lesions of thrombo-angiitis obliterans in the upper extremities. For the past year the patient noticed precordial pressure and lassitude. At times the pressure was intensified into a real pain. There was occasional dyspnea on exertion. Examination revealed poor heart sounds. The apex beat was felt in the 5th interspace. The left border was 12.5 cm. from the midline. No murmurs were heard. Blood pressure was 130/90 mm. in both arms. X-ray examination of the heart and lungs was negative. Electrocardiographic examination showed a thickening of QRS complexes, particularly in Lead III. Their interval measured

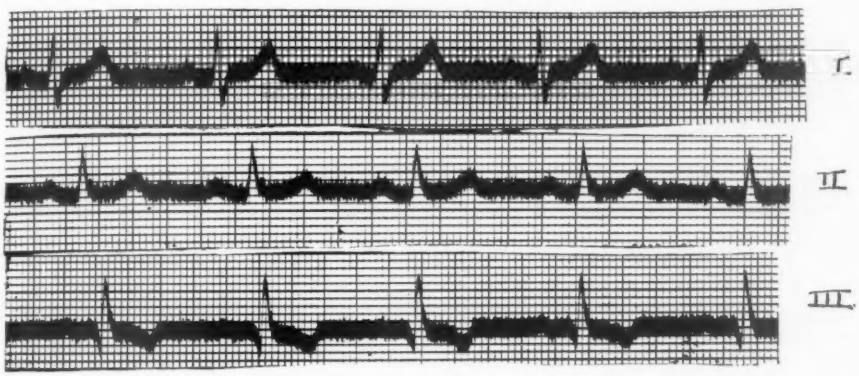

Fig. 1.—A. S. Case No. 20. Moderate thickening of the QRS complexes in all the leads. Their interval measures 0.10-0.12 of a second. T-waves are sharply inverted in Lead III.

0.10-0.12 of a second. The T-waves were sharply inverted in Lead III and had the appearance usually seen after a recent coronary closure.

I. T.—Case No. 27. A man of 40 years whose symptoms of thrombo-angiitis obliterans began at the age of 38. Examination showed marked closure of the arteries of the upper extremities and also of the lower extremities. He had had dyspnea on exertion and palpitation. The heart sounds were weak. X-ray examination showed a peculiar cardiac outline suggestive of myocardial disease. Electrocardiographic examination showed low voltage in all leads and thickening and widening of the QRS complexes, indicative of intra-ventricular conduction defect.

J. F.—Case No. 30. A Russian Jew, aged 31 years, first came under our care January 4, 1926, complaining of pain in the right foot of 15 years' duration. He had been a heavy cigarette smoker for many years. Examination showed bilateral involvement of both lower extremities. His only cardiac symptom when first seen was dyspnea on exertion. At subsequent examinations he began to complain of attacks of precordial pain radiating to the back. He also noticed occasional palpitation. Physical examination showed only a slight enlargement of the cardiac outline particularly toward the left. This was confirmed by x-ray examination. Electrocardiographic examination on January 4, 1926, revealed the fact that the

S-T interval did not reach the iso-electric level in Leads II and III. This phenomenon appeared in the second examination on January 5, 1926. One year later the electrocardiogram showed left ventricular preponderance and a cove plane T-wave

Fig. 2.—I. T. Case No. 27. Thickening and widening of the QRS complexes (intraventricular conduction defect).

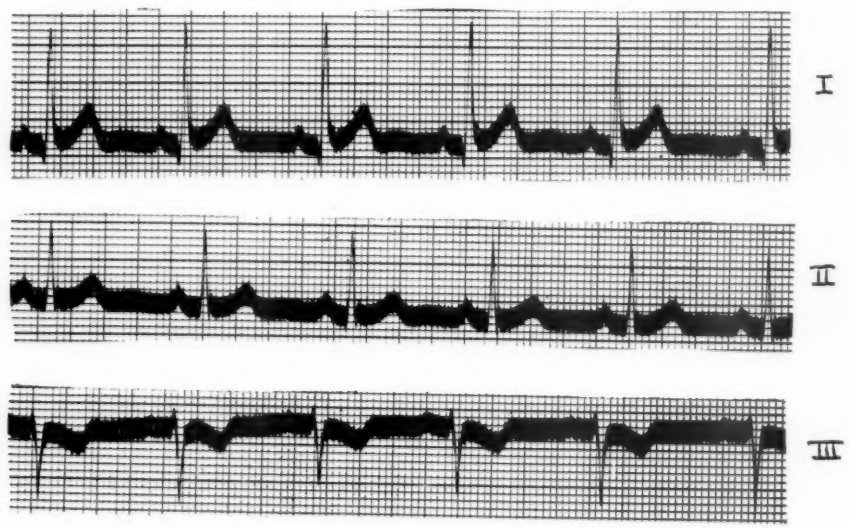

Fig. 3.—J. F. Case No. 30. Left ventricular preponderance. T-waves are sharply inverted in Lead III and are of the cove plane type. S-T transition in Lead I does not quite reach the iso-electric level (myocardial?).

in Lead III. Again it was observed that the S-T interval did not reach the iso-electric level in Lead I.

J. L.—Case No. 50. This patient was a man of 36 years, born in Russia. The onset of symptoms of thrombo-angiitis obliterans occurred in the right leg at the

age of 27. Amputation of this leg was performed 3 years later. The patient subsequently developed lesions in the left leg and in the right upper extremity. He has had frequent attacks of migrating phlebitis in the legs. About 9 years after the

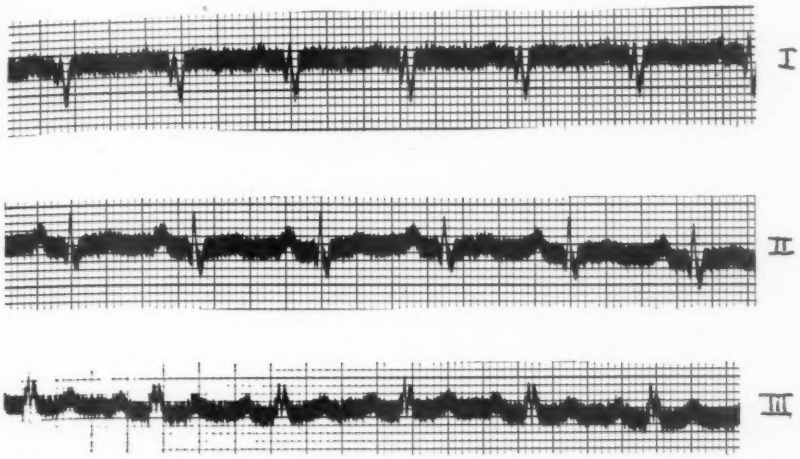

Fig. 4.—J. L. Case No. 50. Right ventricular preponderance. QRS interval measures 0.09 of a second with notching in all leads. Low voltage (intraventricular block).

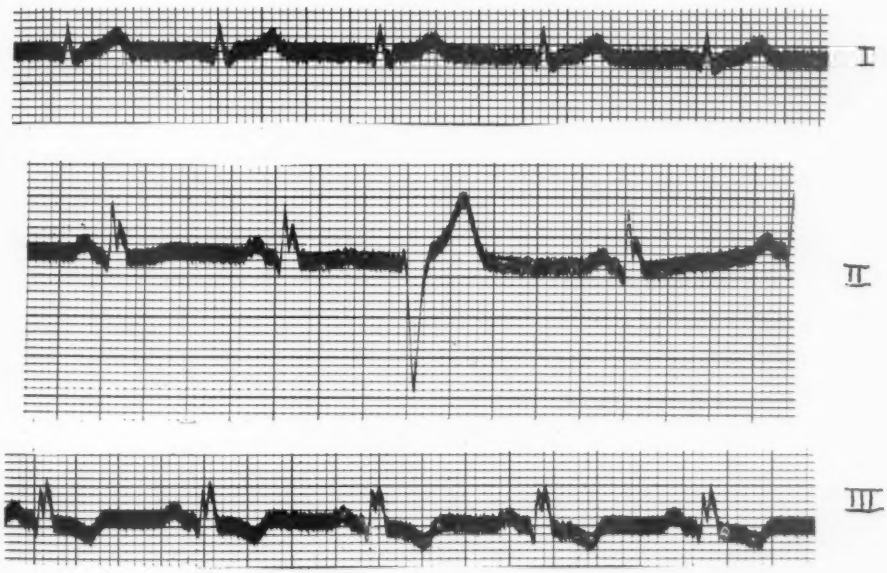

Fig. 5.—Intraventricular conduction defect (arborization block) T_3 negative. Occasional ventricular extrasystole.

onset the patient began to have attacks of sub-sternal pain radiating through to the back. These pains were burning in character and were occasionally associated with vomiting. During some of these attacks the pain radiated down both arms. Soon after this the patient began to complain of dyspnea on exertion. Examination revealed extensive closure of the arteries of both legs and partial occlusion in the

TABLE I

CASE NO.	AGE	CARDIAC HISTORY	CARDIAC EXAM.	B.P.	X-RAY	ECG
1	43	Negative	Negative	130/ 90	Negative	LVP.
9	55	Negative	Negative	145/100	Heart enlarged to left	LVP. T_3 negative. QRS 0.09 second with slight notching
14	36	Negative	A_2 sounds increased	135/ 95	Negative	LVP.
17	44	Precordial pain	Sounds poor at base	120/ 80	Negative	Slight thickening of QRS. LVP.
19	30	Negative	Negative	160/ 95	Negative	Negative
20	52	Precordial pain	Poor heart sounds	130/ 90	Negative	plexes notched T negative in Lead III. QRS com-
21	42	Palpitation	Aortic diastolic	165/105	Negative	Negative
23	44	Negative	Negative	105/ 75	Negative	Low voltage all leads
24	39	Precordial pain	Negative	120/ 90	Negative	Negative
26	33	Negative	Negative	140/100	Negative	Negative
27	39	Dyspnea and palpitation	Negative	125/ 80	Cardiac outline suggestive of myocardial disease	Low voltage. Intraventricular conduction defect
28	47	Negative	Negative	140/ 80	Slight general cardiac enlargement suggestive of myocardial disease	LVP. in Lead II. S-T transition does not reach level
29	33	Moderate dyspnea	Negative	155/110	Negative	LVP.
30	31	Dyspnea on exertion	Negative	135/115	Hypertrophy left ventricle	In Leads II and III S-T does not quite reach iso-electric level
32	37	Precordial distress	Negative	165/ 90	Negative	LVP.
36	27	Dyspnea on exertion	Negative	115/ 85	Negative	LVP.

TABLE I—CONT'D

CASE NO.	AGE	CARDIAC HISTORY	CARDIAC EXAM.	B.P.	X-RAY	ECG
37	41	Negative	Negative	120/ 85	Negative	Negative
39	30	Negative	Negative	135/115	Negative	LVP. T_3 slightly inverted
45	45	Negative	Negative	145/100	Negative	LVP.
50	36	Palpitation and dyspnea	Negative	120/ 85	Hypertrophy and dilatation of left ventricle	Diphasic QRS in Lead I. Slight coving of S-T transition in Lead III
51	39	Negative	Sounds poor at base	140/ 90	Slight general cardiac enlargement	LVP. Inversion of T_3
52	43	Negative	Negative	145/ 90	Negative	Negative
153	52	Precordial pain	Negative	160/100	Negative	Negative
53	40	Negative	Negative	135/ 80	Negative	Negative
54	53	Negative	Negative	140/ 80	Negative	Slight inversion T-waves in Lead III
62	29	Negative	Negative	130/ 85	Negative	Negative
63	34	Negative	Negative	135/ 85	Negative	Negative
65	32	Negative	Poor at base	130/ 70	Negative	Negative
67	35	Negative	Negative	140/ 90	Slight cardiac enlargement	Slight thickening of QRS complexes in all leads
71	44	Negative	Negative	125/ 70	Negative	Negative
84	46	Negative	Negative	155/100	Moderate aortic enlargement	Slight inversion of T_3
89	34	Negative	Negative	130/ 85	Slight enlargement to the left suggesting myocardial disease	T_3 negative. Rate 106

TABLE I—CONT'D

CASE NO.	AGE	CARDIAC HISTORY	CARDIAC EXAM.	B.P.	X-RAY	ECG
100	33	Negative	Poor heart sounds	130/ 80	Negative	Tendency to LVP.
107	62	Negative	Apical systolic	170/ 95	Negative	Negative
116	35	Negative	Negative	135/100	Negative	T_3 inverted
114	42	Negative	Negative	110/ 70	Negative	Negative
117	45	Negative	Negative	130/ 85	Negative	R-waves low in all leads
119	35	Negative	Apical systolic murmur	130/ 80	Negative	Low voltage in Lead III
124	41	Negative	Negative	150/ 80	Negative	LVP.
131	44	Negative	Negative	190/100	Negative	LVP.
132	48	Precordial pain 5 yrs. Dyspnea on exertion	Mitral presystolic and aortic diastolic murmurs	155/ 90	Hypertrophy left ventricle, moderate dilatation of aortic arch	LVP. T_3 negative
133	47	Negative	Negative	140/ 90	Negative	LVP.
137	35	Negative	Negative	125/ 85	Negative	Negative
142	38	Negative	Negative	170/ 90	Negative	Negative
147	47	Negative	Heart enlarged to left	120/ 85	Negative	LVP. T_3 negative
150	40	Negative	Negative	160/110	Negative	LVP. Negative T_3
152	45	Precordial pain. Dyspnea and palpitation	Mitral systolic murmur	150/ 90	Negative	Slight inversion of T_3
156	31	Palpitation and dyspnea	Negative	135/ 85	Negative	Negative
157	56	Precordial pain. Dyspnea	Poor heart sounds	170/110	Negative	Intraventricular conduction defect in Lead III

upper extremities. The heart was not enlarged. Cardiac sounds were all of fair quality. No murmurs were heard. The lungs were clear. X-ray examination of the chest showed moderate hypertrophy of the heart with dilatation of the left ventricle. Electrocardiographic examination showed right ventricular preponderance. QRS interval measured 0.09 of a second with notching in all leads and low voltage. The above indicates intra-ventricular block. (Arborization block of Oppenheimer and Rothschild.)

D. F.—Case No. 157. A Russian Jew, 56 years old. Symptoms of thrombo-angiitis obliterans began at the age of 25 with migrating phlebitis of the right leg. This was followed 4 years later by intermittent claudication, and gangrene of the right leg. Amputation of the right leg was then performed. Ten years ago the patient developed similar pains in the left leg. Gangrene and amputation followed. For the past 5 years he had noticed precordial pain and dyspnea on slight exertion. Electrocardiographic examination showed an intra-ventricular conduction defect (arborization block). T_3 negative. Occasional ventricular extrasystole.

SUMMARY

Fifty cases of thrombo-angiitis obliterans were studied from the standpoint of coronary artery involvement. Five of these cases showed definite clinical and electrocardiographic evidence of myocardial damage, presumably due to coronary artery lesions. Thirty of these cases showed minor evidence, insufficient for the diagnosis of coronary artery damage. Fifteen of these cases showed no clinical evidence of myocardial or coronary artery lesions.

An accurate diagnosis of thrombo-angiitis obliterans of the coronary arteries is permissable only after demonstration of the typical arterial lesion at autopsy.

We wish to thank Dr. Irving Roth, Dr. Emanuel Libman and Dr. B. S. Oppenheimer for their kind cooperation.

HEART DISEASE IN THE ROCKY MOUNTAIN REGION

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VARIOUS writers have suggested the need for data on the incidence and etiology of heart disease in different sections of the country.[1] No such information for the Rocky Mountain region has yet been published. For these reasons certain facts regarding heart disease in Utah, Idaho and Wyoming are presented, and comparison is made with similar data from a few other sections.

Utah, Idaho and Wyoming, lying largely among the Rocky Mountains, are similar in geography, climate and population. The facts available show no significant differences in heart disease between these states. They lie at a high altitude and have a low average annual rainfall despite marked change of seasons. The density of population is very low; according to the census of 1920 there were only eight cities in the three states that had populations of over 10,000. Salt Lake City, the largest of them, had an estimated population in 1929 of 138,000. In 1923 only 8.5 per cent of the population of Idaho, 14.3 per cent of that of Wyoming and 36.2 per cent of that of Utah were classed as urban. This is to be compared with 78.9 per cent for New York and 82.4 per cent urban for Massachusetts.[2] In the Rocky Mountain states there is relatively little poverty or crowded living conditions. The colored population in 1923 comprised less than 2 per cent of the total.[4] The foreign-born population in 1923 averaged less than 17 per cent.[3] Nearly 40 per cent of the population is engaged in agriculture, forestry or animal husbandry.[4] These states present many contrasts with eastern and southern sections, and it was thought of possible interest to learn whether there were any corresponding differences in the heart disease situation.

Mortality.—The cardiac mortality rates for Utah, Idaho and Wyoming are among the lowest state rates in the country. In 1927 they ranked thirty-first, thirty-fifth and thirty-ninth respectively[6] (Fig. 1). Approximately the same relative positions held true for 1921,[5] 1923[2] and 1925.[5] These relatively low rates are not peculiar to heart disease, as the rates in the three states were also comparatively low for the other major causes of death and for all causes.

It would be of interest to know whether the proportion of deaths from each etiologic type is the same in the states with high and low cardiac mortality; whether the differences between states in total cardiac mortality could be associated with corresponding differences in only one of the etiologic types such as the rheumatic or the arteriosclerotic. Unfortunately mortality statistics as at present reported

do not furnish such data. A suggestive correlation is obtained by comparing for each state the proportion of cardiac deaths occurring at the younger ages with the total cardiac mortality. The year of 1923 was chosen as presenting for most states a fair representation of the mortality trend. The deaths under the age of forty-five years were arbitrarily chosen because mortality and population statistics were readily available for this age group. Cardiac deaths under forty-five years of age indicate roughly enough, it is true, deaths largely from rheumatic heart disease in contrast with the deaths over forty-five years from the degenerative types of heart disease. Such a comparison showed that in general the higher the total cardiac mortality rate, the lower the proportion of cardiac deaths under the age of forty-five years (Fig. 1). (An approximately parallel but lower curve could be drawn for deaths under thirty-five years of age.) The significance of such a comparison becomes less, however, if we compare the cardiac death rate under forty-five years per 100,000 population living under the age of forty-five years with the total cardiac mortality rate (Fig. 1). It now becomes apparent that the age distribution of the living population explains at least in part the supposed inverse ratio between total cardiac mortality and cardiac mortality under the age of forty-five years. It is curious to note the relatively high cardiac mortality under the age of forty-five years in the states of Louisiana and Florida where rheumatic heart disease is supposed to be less frequent than in northern states.

As a corollary to this it seems that there is a significant relation between the total cardiac mortality of each state and the living proportionate population over the age of forty-five years in each state (Fig. 2).

It has been shown that in the registration area the urban cardiac mortality rate has remained each year appreciably higher than the rural one.[5] So it is of interest to note that there is a rough correlation between the cardiac mortality of the states and their percentage urban population (Fig. 2). No such relation could be shown between mortality rates and density of population.

In Utah the cardiac mortality by years has been rising in a manner more or less similar to that of other states and of the registration area (Fig. 3). Idaho and Wyoming have been included in the registration area for too short a period to justify comparison. The mortality rate for Salt Lake City has been rising as in other cities of the country.

As elsewhere the urban cardiac mortality rates of Utah, Idaho and Wyoming are higher than the rural ones. In each of the three states and in Salt Lake City as elsewhere heart disease is the principal cause of death.

Etiology.—In order to secure data regarding the etiology of heart disease in this section of the country a study has been made of 1000

Fig. 1.—Mortality rates by states from heart disease (Code 87-90).

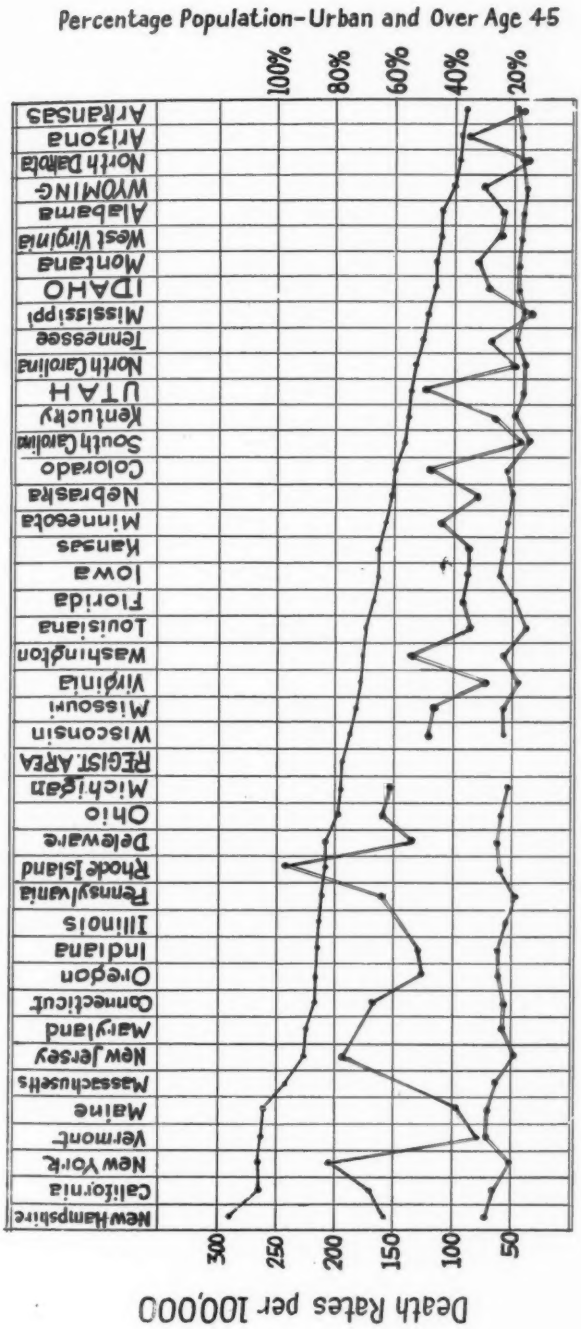

Fig. 2.—Mortality rates by states for heart disease, compared with urban population and population over the age of forty-five years (Code 87-90).

cases of heart disease or disorder occurring in this Rocky Mountain region. All the cases were studied by myself, by my associate Dr. W. R. Tyndale or by both of us, thus insuring uniformity of diagnosis. The diagnostic criteria were those proposed by the Heart Committee of the New York Tuberculosis and Health Association.[7] The cases were consecutive ones except that of the earlier records those were excluded in which the history and findings described did not justify the diagnosis recorded. A rough check showed that the exclusion of such records did not affect the final figures. A high percentage of the cases had repeated examinations and electrocardiographic and x-ray studies. The

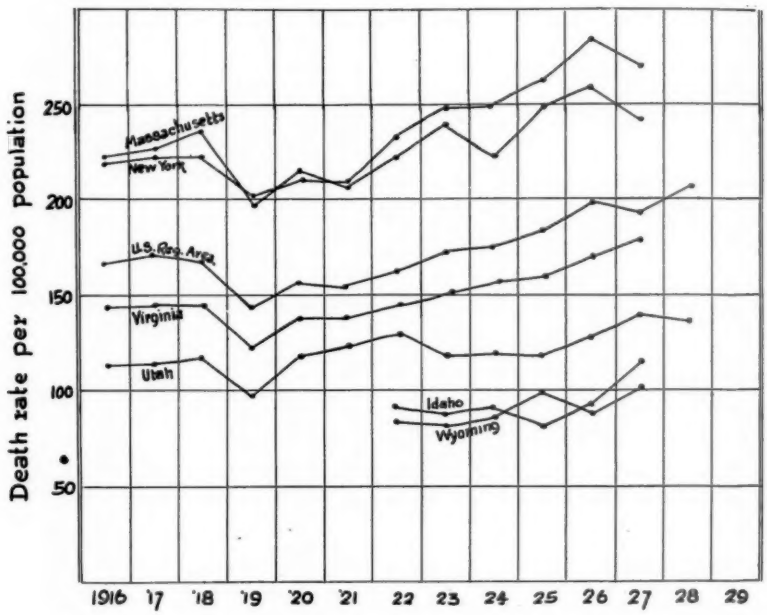

Fig. 3.—Heart disease death rates of certain states, 1916 to 1927.

cases represent consultant practice, ordinary private practice in home and hospitals, charity service at the Latter-Day-Saint Hospital in Salt Lake City and cases in the teaching of medical students at the Salt Lake County Hospital. As Salt Lake City is the medical center for Utah, southern Idaho, southern Wyoming and eastern Nevada a fair percentage of the cases were residents of Utah (88.5 per cent). Nearly one-half were residents of rural districts (Fig. 4) which corresponds fairly closely to the distribution of the population between urban and rural districts. These considerations, together with a comparison with some hospital statistics to be referred to later, seem to show that the series is truly representative of cardiac disease in this section.

Etiologic Type	Total	Sex		Age								Residence										Structural Defect – Valve Defect.																Mechanism				Failure	
		Female	Male	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+	Salt Lake	Ogden & Provo	Utah Rural	Idaho Urban	Idaho Rural	Wyo. Urban	Wyo. Rural	Nev. Urban	Nev. Rural	Other	A.R.	A.S.	A.R. + A'S	M.R.	M.S.	M.R. + M.S.	A.R. + M.R.	A.R. + M.S.	A.R. + A.S. + M.R.	A.R. + M.R. + M.S.	A.R. + A.S. + M.R. + M.S.	Peric.	Coron. Occl.	Auricular Fibrillation	Ventricular Failure	Thromboses	Rheumatic Tachycardia	Acquired	Congenital
Rheumatic	361	144	217	35	94	113	68	35	13	3	0	203	14	110	0	24	0	8	0	0	2	1		1	121	18	166	12	3	3	31	5	6		40	7	20	3	4	68
Rheumatic + Cardiac Neurosis	27	7	20	0	7	6	9	4	1	0	0	18	0	6	0	3	0	0	0	0	0				19		5	1		2					2		1			1
Rheumatic + Thyroid	6	0	6	0	0	0	4	2	0	0	0	1	1	3	0	1	0	0	0	0	0				2		4								1					3
Rheumatic + Hypertensive	8	1	7	0	0	1	1	1	4	1	0	1	2	5	0	0	0	0	0	0	0				3		5								2		1		2	5
Rheumatic + Arteriosclerotic	6	4	2	0	0	0	0	0	0	5	1	4	0	1	0	1	0	0	0	0	0				2		3	1							4					3
Rheumatic + Congenital	1	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0				1	Pulmonary Stenosis (1)											20	4		
Arteriosclerotic	156	95	61	0	0	0	0	4	34	80	38	75	6	60	2	6	0	3	0	2	4	1	4		5								4		11	10	2		55	44
Arteriosclerotic + Hypertensive	29	11	18	0	0	0	0	1	4	20	4	12	3	12	0	1	0	1	0	0	0				1			1							6	1	10	1	8	11
Arteriosclerotic + Thyroid	2	0	2	0	0	0	0	0	0	2	0	2	0	0	0	0	0	0	0	0	0															1				
Arteriosclerotic-Syphilitic	1	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0																			
Hypertensive	98	17	81	0	1	2	7	15	35	32	6	48	0	41	0	4	0	3	0	1	1														5	9			15	30
Hypertensive Thyroid	1	0	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0																1			
Hypertensive Syphilitic	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0																		1	1
Thyroid	76	7	69	0	4	13	17	17	20	5	0	24	1	40	1	8	0	1	0	0	1																6		5	33
Unknown Etiol	67	39	28	1	1	4	9	20	29	2	1	52	2	25	0	3	1	1	0	0	3				3								5		6	3	3		18	19
Syphilitic	8	8	0	0	0	0	1	3	3	1	0	4	0	2	0	0	0	1	0	0	1	6			1									1	1				6	5
Congenital	8	3	5	5	3	0	0	0	0	0	0	5	0	2	0	1	0	0	0	0	0				Pulmonary Stenosis (5)														2
Congenital + Toxic	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0																1			*
Toxic	4	3	1	1	0	1	1	0	1	0	0	3	0	1	0	0	0	0	0	0	0																1			2
Anemic	3	0	3	0	0	0	0	2	1	0	0	0	0	2	0	1	0	0	0	0	0																1			1
Subacute Bact. Endocarditis	2	2	0	0	0	0	1	1	0	0	0	2	0	0	0	0	0	0	0	0	0						1													1
Myxoedema	1	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0																			1
Total "Organic"	867	344	523	42	111	140	120	106	147	151	50	435	29	312	3	54	1	18	0	3	12	8	4	1	158	18	184	15	3	5	31	5	11	5	83	31	67	8	114	230
Irritable Heart	37	22	15	0	2	13	9	11	1	1	0	22	0	9	0	2	0	0	0	3	1																32	15		
Cardiac Neurosis	96	43	53	0	12	36	34	12	1	1	0	54	4	20	0	8	0	5	0	3	2																21	4		
TOTAL	1000	409	591	42	125	189	163	129	149	153	50	511	33	341	3	64	1	23	0	9	15	8	4	1	158	18	184	15	3	5	31	5	11	5	83	31	120	27	114	230

Fig. 4.—One thousand cardiac cases.

The series included 867 cases of organic heart disease and 133 cases of irritable heart or cardiac neurosis. Cases with only sinus arrhythmia or functional murmurs were not included unless a diagnosis of cardiac neurosis or irritable heart was justified by history or other findings. Angina pectoris was not listed as a separate classification. Most of the cases presenting true angina were included under either the arteriosclerotic, hypersensitive, syphilitic or rheumatic groups. The others largely fell into the classification of unknown etiology. The same treatment was accorded auricular fibrillation as a diagnosis. A number of cases were due to more than one etiologic factor (Fig. 4).

The structural defects found, certain changes in mechanism, and the number of each type showing failure are shown in Fig. 4, but no discussion of these considerations will be presented.

In order that proper comparison may be made with similar series of cases reported from other sections of the country, only the cases of organic heart disease are included, and in view of the dual etiology of many cases each etiologic factor has been considered as an entity. For the series this gave 867 cases with 922 etiologic factors. Making a similar change in the figures of some other reports, a comparison, limited somewhat by differences in classification, was possible between the present series of cases and those reported by a few other writers (Table I).

TABLE I

	VIRGINIA[8]	TEXAS[9]	NEW YORK CITY[10]	NEW ENG.[11]	ROCKY MOUNTAINS
No. cases	300	915	1000	2421	867
No. etiol. factors	423	915	1051	3259	922
Rheumatic	15.6%	7.3%	42.7%	29.3%	44.0%
Arteriosclerotic	32.4	13.7	22.3	26.3	21.1
Hypertensive	32.6	47.7		21.7	14.9
Syphilitic	7.8	19.3	8.6	2.7	1.1
Thyroid	2.6	1.3		2.1	9.3
Angina pectoris	6.6	2.3		10.9	
Congenital	.7	.7		1.1	1.1
Unknown	1.6		17.8	2.2	7.3
Subac. bact. endoc.		1.5		1.4	.2
Miscellaneous		1.3	8.6	1.6	.9
Unclassified		4.9			

From Table I it is evident that the proportion of rheumatic cases is high in the Rocky Mountain region in comparison with the other sections considered. As remarked previously in the discussion of mortality statistics, the proportion of the living population under the age of forty-five years is high in this Rocky Mountain area. This may in part account for the high rheumatic figure, yet Texas and Virginia with their low incidence of rheumatic heart disease have age distributions of the population very similar to that of Utah, Idaho and Wyoming.

That thyroid heart disease is relatively more frequent in the Rocky Mountain section is not surprising as this is an endemic goiter area.

The low incidence of the syphilitic type is of interest. That the figure given is not due to error in diagnosis seems to be shown by a comparison of the mortality from syphilis and from aneurysm in the Rocky Mountain states and in other states. In Utah, Idaho and Wyoming the death rates from each are well below that of the registration area. This may be partly explained on the small colored population. A further check on the accuracy of the incidence of syphilitic heart disease will be referred to later in connection with some hospital statistics.

The age distribution of the different etiologic types (Fig. 4) was quite similar to that reported by Wyckoff and Lingg.[10] The data available did not permit conclusions regarding the relative length of life at high and low altitudes. Such information would be desirable.

A comparison of the etiology of heart disease in the urban and rural portions of the series of cases was of interest (Table II).

TABLE II

ETIOLOGY OF HEART DISEASE IN URBAN AND RURAL PATIENTS

	RHEUMATIC	ARTERIOSCLEROTIC	HYPERTENSION	SYPHILITIC	THYROID	CONGENITAL	UNKNOWN	SUBACUTE BACTERIAL ENDOCARDITIS	MISCELLANEOUS
	409	194	137	10	85	10	67	2	8
Urban (496)	49.4%	20.8%	13.1%	1.0%	6.0%	1.2%	7.0%	.4%	.8%
Rural (412)	39.3%	20.6%	17.0%	.9%	13.1%	.9%	7.4%		.9%

Only the rheumatic, arteriosclerotic and hypertensive groups are in number large enough to merit such comparison. There is a suggestively larger percentage of the rheumatic type in the urban patients. But no consideration has been given to changing residence.

The sixty-seven cases listed as "etiology unknown" raise many questions regarding possible causes of heart disease. Table III shows the possible etiology of these cases. Fourteen were probably due to one of the common etiologic factors, but as these were not clearly established it was thought best still to consider them of unknown etiology. Many of the others occurred in association with or following acute or chronic infections, but to state that they were certainly due to such infections would expose one to the *post hac propter hac* fallacy. The possibility of such error is best exemplified in the nine cases whose supposed onset followed influenza. None of these had had a complete examination (including electrocardiogram and x-ray) prior to the influenza; only such study would exclude the possibility that the influenza had merely served to bring a latent heart disease to consciousness.

TABLE III

HEART DISEASE OF UNKNOWN ETIOLOGY, SIXTY-SEVEN CASES

1. Probably one of recognized etiologic groups				14
Rheumatic	3	Syphilitic	1	
Thyroid	3	Acute bacterial	1	
Arteriosclerotic	3	Congenital	1	
Hypertensive	2			
2. Possibly secondary to acute infectious disease				11
Influenza	9	Puerperal sepsis	1	
Typhoid	1			
3. Probably secondary to pulmonary disease				11
Pneumonia	6	Tuberculosis	2	
Asthma	2	Pneumonokoniosis	1	
4. Possibly secondary to chronic infections				5
Chronic sinusitis	3	Chronic cholecystitis	2	
5. Possibly toxic				2
Nephritic	1	Tobacco	1	
6. In association with obesity				4
7. No cause apparent				20

Some Hospital Statistics.—Hospital statistics on the incidence of heart disease have little value because of the general lack of uniformity in diagnostic criteria. They are presented here to serve as a rough check on the 1000 other cases discussed.

The Latter-Day-Saint Hospital in Salt Lake City is the largest hospital in the three Rocky Mountain states. Its admissions come from all three states. During the three years 1927, 1928 and 1929 there were 16,519 admissions of which 477, or 2.9 per cent, had a diagnosis of a heart disease or disorder. The numerous and various cardiac diagnoses were considered from an etiologic standpoint and duplication was eliminated. Such diagnoses as mitral stenosis, chronic endocarditis, valvular heart disease, etc., were considered as probably rheumatic. Where no etiologic factor was apparent from the diagnosis, the cases were listed as cause unknown or unspecified. In this manner 525 etiologic factors in the 477 cases were tabulated and a comparison was made with my own series. Cardiac neurosis and irritable heart were included in each instance.

TABLE IV

COMPARISON OF AUTHOR'S AND HOSPITAL SERIES

	RHEU.	HYPER. ART. "CHR. MYOC."	SYPH.	CONG.	THYR.	CARD. NEUR.	UNK.	MISC.
Author's series 1000 cases 1055 etiologic factors	38.8%	31.3%	.9%	.9%	8.0%	12.6%	6.3%	.9%
Hospital series 477 cases 525 etiologic factors	40.4%	40.6%	1.7%	1.7%	3.4%	.4%	8.4%	3.5%

In view of the difficulty of evaluating the etiology of the hospital series the agreement seems close enough to serve as a check on my series.

COMMENT

Mortality statistics of heart disease in three of the Rocky Mountain states are presented. In contrast with other states they show relatively low rates. It is suggested that this lower mortality may be more the result of differences in age distribution of the population and a low percentage of urban life than of geographic or climatic conditions. Is it possible that the rising cardiac mortality throughout the United States is also partly the expression of the shift of the population from rural to urban life? It seems that the adjusted mortality in the lower age group does not show the wide state variation that the total mortality shows. Comment is made regarding the relatively high mortality in the lower age group in such southern states as Louisiana and Florida.

In studying 1000 cases of heart disease occurring in the Rocky Mountain states in comparison with other states the incidence of rheumatic heart disease seemed relatively high; it is again suggested that this may be partly due to the age distribution of the population. The thyroid heart disease incidence is high in contrast to other sections. The incidence of syphilitic heart disease is low, possibly at least partly due to the small colored population. The incidence of rheumatic heart disease seemed significantly higher in urban than in rural patients.

Reference is made to possible etiologic factors in the groups whose cause is listed as unknown.

Some hospital statistics are reported to serve as a check on my series.

No peculiarities in the etiology of heart disease were found that could be ascribed to the unique geographic or climatic conditions of this region except the high rheumatic and thyroid incidence.

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ANEURYSM OF THE THORACIC AORTA

Report of a Case Presenting Some Unusual Features*

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ALTHOUGH the literature contains accounts of many interesting and unusual syphilitic aneurysms, the case recorded in this paper seemed worthy of consideration, since it presented interesting and unusual clinical and pathological features, all of which are rarely to be noted in a single patient.

CASE REPORT

A fifty-seven year old, white, widowed saleman was admitted to the University Hospital on October 21, 1928, complaining of a swelling of seven years' duration over the upper, right anterior chest.

Family History.—The family history was of no significance. He was married thirty-three years before and had one child living and well. His wife died five years before; the cause of her death was not determined.

Past History.—His general health had been good. During childhood he had measles, mumps, scarlet fever and whooping cough. Thirty-five years ago he had a discharge from the urethra. Four years later there were symptoms of urethral obstruction which were relieved by treatment. He denied having had a penile lesion or any secondary manifestations of syphilis.

Present Illness.—The patient was in good health until seven years before when he noticed a mild, burning pain in the region of the right shoulder and over the right, upper, anterior chest. The pain was not related to exercise, excitement or the taking of food; its intensity, greater at some times than at others, was decreased by assuming various positions in bed. There was no definite position, however, that would always relieve the distress. The sensation was almost continuous for a period of eight weeks and at the end of that time there appeared in the region of the right nipple a small, nontender swelling, the size of an English walnut. A physician sent him to a hospital and on September 21, 1921, a roentgenogram of the chest was made† (Fig. 1). The x-ray diagnosis was aneurysm of the aorta. During the following six years he had occasional attacks of the burning previously described, coming on every three or four weeks and lasting not more than two or three days.

For the past year the pain had been more severe and intense, but had not been continuous. During this period the pain started in the region of the right nipple and frequently radiated down the right arm as far as the elbow. Occasionally he was relieved by shifting his position in bed, although he was not sure that one particular position was more effective in relieving the distress. The swelling on the

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†We are indebted to Dr. C. F. Potter, Roentgenologist to the Crouse-Irving Hospital, for permission to reproduce this film.

chest increased only slightly in size until about six months before when it was found to be the size of a hen's egg. One month before it had increased to the size of a large apple, and the patient claimed that the tumor has doubled in size in the past two weeks. Two months before he consulted the Syracuse Free Dispensary. Potassium iodide was prescribed, the first antisyphilitic treatment he had received.

Other symptoms were: general weakness and gradual loss of weight during the past six years; slight twitching of the right hand associated with the attacks of chest pain for three months; marked dyspnea whenever the chest pain was severe; a moderate amount of cough with an occasional streak of blood in the sputum for five or six weeks.

Physical Examination.—The patient was a well developed, rather poorly nourished white man of fifty-seven years, sitting up in bed, breathing quietly, apparently in no acute distress. His mouth temperature was 98°, radial pulse 80 beats per minute, respirations 19 per minute. The left radial pulse had more volume than the right.

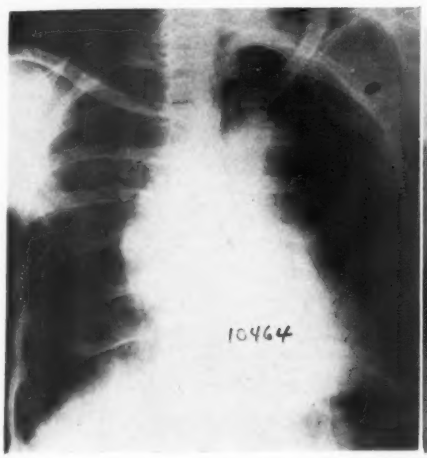

Fig. 1.—Roentgenogram of the chest made on September 21, 1921, which reveals aneurysm of ascending aorta.

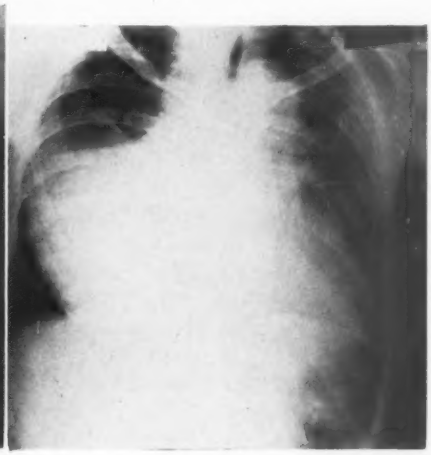

Fig. 2.—Roentgenogram of the chest made on November 22, 1928, which reveals an area of increased density occupying the middle right lung field. The shadow of the ascending aorta cannot be separated from this area of density.

The blood pressure on each arm was 102/66 mm. Slight cyanosis of the lips and pallor of the skin were noted. The right pupil was larger than the left and reacted less readily to light, both pupils, however, reacting sluggishly to the reflex.

Over the right, upper anterior chest was a slightly tender, pulsating, expansile tumor, the size of a large grapefruit. The measurements of the mass were taken in the following manner: V (vertical), measured from the right midclavicular point to the lowest point of the tumor; T (transverse) measurements were taken from the midsternal line to the farthest lateral point; E (elevation), the elevation measured above the level of the sternum.

The vertical measurement was 17 cm.

The transverse measurement was 15 cm.

The elevation measurement was 5 cm.

At the upper medial aspect of the pulsating mass was a softer, and more tender, fluctuating portion which was more elevated than the surrounding area. The left border of cardiac dullness was 13.75 cm. from the midsternal line in the fifth

interspace. The apex impulse was not seen or felt. The heart sounds were of good quality, apex rate 80 beats per minute and regular. There was a loud, blowing systolic murmur heard over the precordium, with the maximum intensity noted at the apex. There was no abnormality of the second sound. The heart sounds and the systolic murmur could be heard over the pulsating mass.

Examination of the lungs revealed a few moist râles at the left base posteriorly. There was clubbing of the fingers with moderate cyanosis of the nail beds. The deep reflexes were equal and active.

Laboratory Studies.—Red blood count, 4,800,000; hemoglobin, 60 per cent (Sahli); white blood count, urine, blood chemistry and renal function were normal. Complement-fixation test for syphilis: The fixation of complement was complete with the cholesterinized and the noncholesterinized antigens.

A fluoroscopic examination of the chest revealed "a pulsating mass, the size of a grapefruit, in the anterior portion of the mid right lung field, apparently arising from the ascending aorta." A roentgenogram of the chest showed a round shadow. The trachea and heart were displaced to the left (Fig. 2).

Clinical Course and Progress.—The mass gradually increased in size, and the pain became so severe and intense that for the greater part of the time opiates were required. Two months after admission the measurements of the tumor were: (V) 22 cm.; (T) 16 cm.; (E) 8 cm. It was noted that the skin over the mass in the region of the nipple was blanched with a small area of ecchymosis surrounding it.

On January 24, 1929, three months after admission, the measurements of the tumor were: (V) 26 cm.; (T) 25 cm.; (E) 11 cm. The circumference of the tumor around its base on the chest wall was 70 cm. The patient was very weak. The blood pressure reading on the right arm was 104/74 mm., on the left 118/88 mm. There was dullness at the right base posteriorly, and the breath sounds over this area were considerably diminished. Marked dyspnea was present. The radial pulses were of poor quality but synchronous. The right radial pulse was almost imperceptible. The patient grew weaker, and on the morning of February 9 it was noted that he had marked inspiratory dyspnea. On February 10, 1929, the patient died.

*Necropsy.**—"Body is that of a fairly well developed, poorly nourished adult male, 171 cm. in length. There is a large, rather irregular mass on the anterior surface of the right chest wall. This mass is soft and fluctuating and measures 65 cm. around its base, 20 cm. in diameter in one direction, 22 cm. in diameter in the other direction and 11 cm. in height. The skin is pulled tightly over this mass and is adherent to it.

"On opening the body the usual midline incision is made from the upper part of the sternum to the symphysis, exposing the peritoneal cavity. On the left side the muscles and skin are reflected from the chest wall as usual. On the right side the skin is reflected from over the mass by making an incision below the mass at about the level of the costal margin, extending from the midline incision upward and backward to about the mid-axillary line. The skin is then reflected." The peritoneum is without evident lesion.

"On opening the chest wall on the left side as usual, the ribs are cut through at the junction of the cartilages. On the right side the ribs are cut through just beneath the skin and soft tissues. The line of incision is carried upward and backward to the intercostal space between the 2nd and 3rd ribs and then the intercostal muscles in this space are cut up to the clavicle. The pleural cavities are

*This is a partial report of the complete autopsy performed on February 11, 1929, by Dr. H. G. Weiskotten, Dean of the College of Medicine.

examined and then the viscera removed in one mass. The organs are then dissected away and examined, leaving the aorta, heart and pericardial cavity in relation to one another.

"Pleural Cavities: The right pleural cavity contains about 300 c.c. of a clear amber-colored fluid. There is no free fluid in the left cavity. Pleural surface of both lungs is fairly smooth and glistening. The right lung is somewhat collapsed, the mass and fluid occupying almost the entire right pleural cavity.

"Lungs: Weight not unusual. Surface of both lungs is somewhat reddish in color and smooth and glistening. On section the cut surface is not unusual. On pressure there can be expressed a moderate amount of reddish and grayish frothy fluid."

Spleen, liver, gall bladder and ducts, pancreas, kidneys, adrenals, and organs of the pelvis were not remarkable.

"Mass, Heart and Aorta: After removing the above described organs, the heart and aorta, which are left attached together, are examined. The aorta is opened throughout its entire length, beginning in the abdominal aorta and extending into the left ventricle. When this is done it is found that the mass is in direct

Fig. 3.—Appearance of aneurysm, illustrating size and elevation.

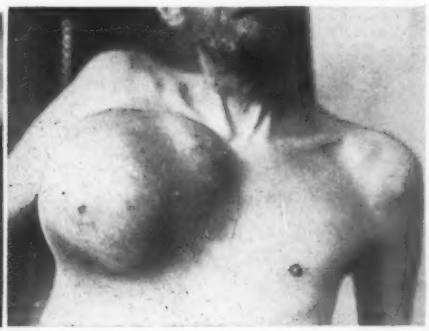

Fig. 4.—Note relative size of aneurysm and chest wall.

continuity with the first portion of the aorta 6 cm. above the heart, there being an opening between the mass and the aorta at this point, measuring about 3 × 4 cm., across, allowing the blood free circulation into the mass. Between this opening and the heart there was another small pouching of the aorta, measuring about 3 cm. across and about 2 cm. in depth. A portion of the wall of the mass is removed, beginning at the aorta and extending down one side of the mass, clearly demonstrating that there is a communication between the aorta and the mass. Most of the lumen of this mass is filled with organized blood clot, but the center is composed of fluid blood and post-mortem blood clot. On further examination it is found that the mass had eroded through the ribs and had extended to the external surface. The entire specimen was preserved and there was no further examination of the heart or pericardial cavity.

"*Anatomical Diagnosis.*—Aortitis; Aneurysm of the first portion of the aorta; edema and congestion of the lungs; some acute nephritis; right sided hydrothorax with collapse of the lung; marked generalized arteriosclerosis."

COMMENT

The particular features of interest in this case seemed to be the size of the lesion, its duration and the termination.

Size.—Rarely are aneurysms seen that have reached such a tremendous size as the one described. Osler[1] states that "when perforation of the chest occurs, the size of the adult head may be reached, and with its contents the aneurysm may weigh five or six pounds. Broadbent[2] declares that "aneurysm of the ascending aorta may attain very great size, sometimes being as large as a child's head." Figs. 3 and 4 show the tumor protruding through the anterior chest wall. Fig. 5 shows the post-mortem specimen, illustrating the relative size of the aneurys-

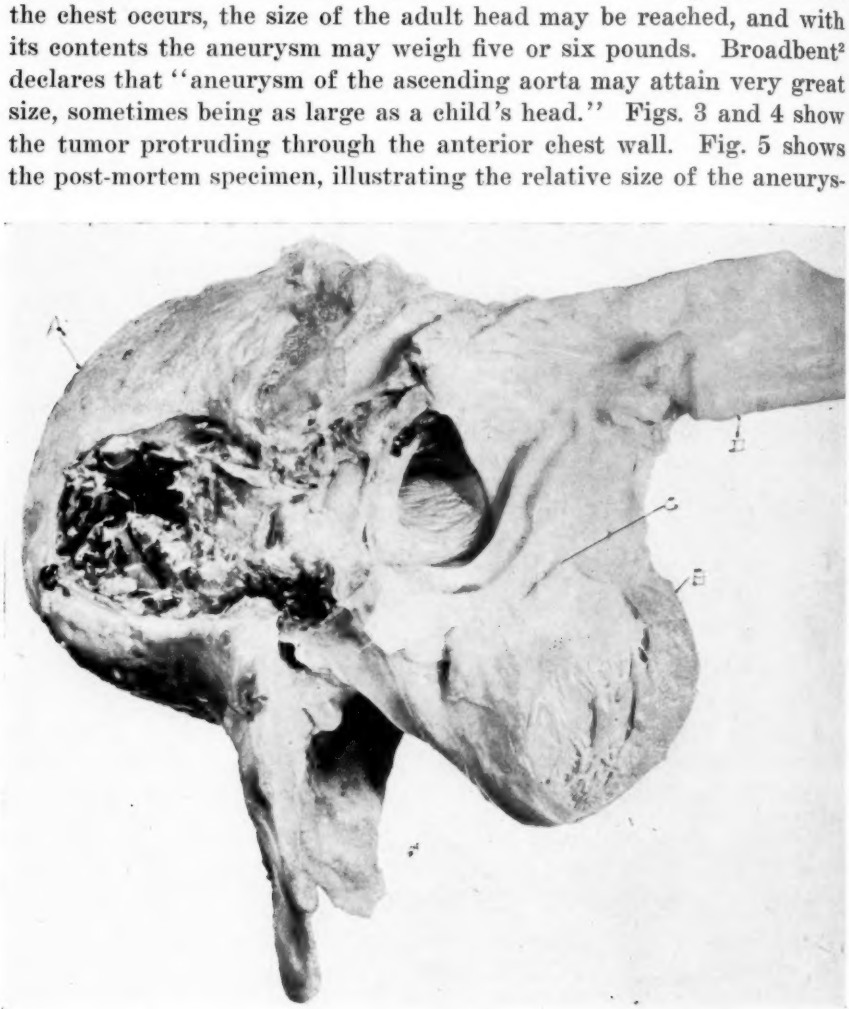

Fig. 5.—Note the relative size of the aneurysmal tumor (*A*) and the heart (*B*), also the aorta cusps (*C*) and the aorta (*D*).

mal tumor and the heart of normal size. It will be recalled that two weeks before death the tumor on the anterior chest wall measured 70 cm. in circumference and protruded 11 cm. in front of the sternum.

Duration.—A most unusual feature of this case was its duration. Colt[3] found the average clinical duration in 101 cases to be 19.6 months. Lemann's[4] series of 84 cases includes no case of more than 48 months. Broadbent[2] states: "When situated in the ascending portion of the arch above the pericardium, the patient may live for some years without experiencing much inconvenience from it, especially if the aneu-

rysm extends forward and makes its way through the chest wall." Cabot[5] believes that when symptoms finally appear they usually lead to death within two years. Sailer[6] reported a patient who lived for three and one-half years after wiring and then died of unwarranted exertion. In the case presented we have definite knowledge of the existence of the aneurysm for at least seven years. A further point of interest is that it was not until the aneurysm had made its external appearance on the anterior chest wall that the patient was examined and the nature of his lesion determined. The roentgen-ray appearance of the aneurysm in September, 1921, is shown in Fig. 1. The roentgenogram of the chest in November, 1928, is illustrated in Fig. 2. For six and one-half years the size of the external tumor remained practically stationary, according to the history given by the patient.

Termination.—When one considers the size and duration of the tumor, it seems remarkable that there was no point of rupture, either externally or internally. When rupture occurs, it is more likely to be internal. However, one could hardly fail to have been impressed by the thinness of the stretched skin over the large, protruding, pulsating mass. Those who examined the mass after it had reached this tremendous size were indeed reluctant to palpate the lesion lest the slightest pressure precipitate what seemed almost inevitable.

There is general agreement[5, 7, 8, 9, 10, 11] in the view that whereas from one-fourth to one-half of all cases of aneurysm terminate in rupture it is very rare to have the rupture occur externally. In the case described in the present communication it has been pointed out that there were no clinical signs or symptoms of rupture; the post-mortem examination also failed to reveal any point of rupture.

SUMMARY

A case of thoracic aneurysm presenting some unusual features is reported. Previous to death the protruding aneurysmal tumor measured 70 cm. around its base and was elevated 11 cm. above the level of the sternum, illustrating the fact that aneurysms of the thoracic aorta may reach a size larger than is generally appreciated. Evidence is presented to show that the aneurysm was present for more than seven years. Clinical and post-mortem examinations failed to reveal any point of rupture in the aneurysmal wall. The fact that this type of termination may occur in an aneurysm of unusual size and duration should be appreciated by the physician when considering prognosis.

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Department of Clinical Reports

ARTERIOVENOUS ANEURYSM BETWEEN AORTA AND SUPERIOR VENA CAVA. CASE REPORT*

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SINCE 1832 when Beevor[1] described the first example of arteriovenous aneurysm between aorta and vena cava, about sixty cases have been reported in the literature. The first correct clinical diagnosis was apparently made by Mayne[2] in 1853. Pepper and Griffith[3] were the pioneers in this country to direct attention to this interesting and unusual condition. In 1890 they were able to collect and analyze forty-three cases, establishing the diagnostic criteria for its clinical recognition. Except for the incomplete surveys of the literature by Fussell[4] and by Herrick,[5] very little has been added to our knowledge of the subject since that time. We have been fortunate to observe and autopsy a typical example of this condition, and because of its rarity we are publishing the case.

CASE REPORT

A. L., a Pole, thirty-eight years of age, a truckman by occupation, was admitted to the Gouverneur Hospital August 30, 1929, complaining of headache, dizziness and difficulty in breathing.

His past history was entirely negative and he denied venereal disease by name and symptoms. He had been performing his usual strenuous work in his capacity as a truckman when with absolutely no prodromal symptoms he was suddenly seized with intense headache and dizziness. Associated with these were a choking sensation, great difficulty in breathing and a frequent distressing cough. His face and neck had at the same instant become markedly swollen and deep blue in color. He had vomited once before his admission.

On physical examination, he presented a striking and unique appearance. The outstanding feature was the peculiar disproportion between the upper and lower halves of his body. His face, neck, upper extremities and the upper half of his chest were not only greatly swollen and pitted on pressure but were extremely cold and cyanotic. The upper extremities were least involved and both the edema and cyanosis stopped abruptly at the level of the fourth rib. He was markedly dyspneic and orthopneic and visibly in great distress. The conjunctivae were greatly congested. The pupils, though regular in outline, reacted sluggishly to light and in accommodation. The mucous membranes of his nose and mouth were cyanotic, as were his ears. His neck could only be described as bull-like in character, and, although the veins were engorged, no pulsation could be discovered. His chest was difficult

*From the Medical Service of the Gouverneur Hospital.

to examine because of the edema. The apex impulse of the heart was located in the seventh left interspace in the midaxillary line. The heart was also enlarged to the right. The manubrial dullness was increased, especially beneath the right clavicle, but the exact extent was difficult to determine. A systolic thrill was palpable at the base, and a very loud murmur was heard over the entire chest, louder, however, over the aortic region. The murmur was of a peculiar character. It was continuous through both systole and diastole, but became markedly intensified with each systolic contraction. It was high pitched and slurring in quality, and completely replaced the first sound. The second sound was inaudible. The pulse was of the Corrigan type, and the blood pressure in each arm was as follows: right, 190/0 mm.; left, 176/20 mm. Moist râles were heard over both bases of the lungs.

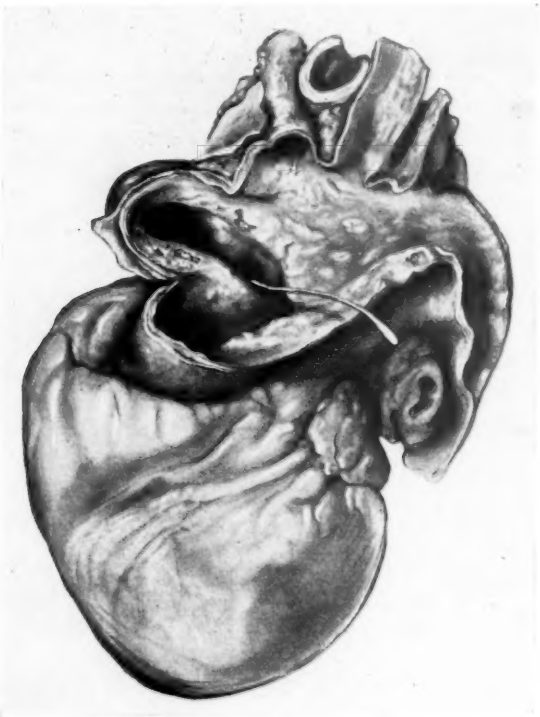

Fig. 1.—Arteriovenous aneurysm, anterior view.

The liver and spleen were not palpable. The lower extremities exhibited no abnormalities and were in marked contrast to the upper. The reflexes were normal and no pathological reflexes were present.

The laboratory findings were as follows: Urine: albumen 1 plus; a few hyaline casts. Blood count: R.B.C. 7,400,000; W.B.C. 17,200; polynuclear cells 63; lymphocytes 31; mononuclears 6. Wassermann: 3 plus. Blood Chemistry: N.P.N. 128; sugar 105.

The clinical course was extremely brief. He gradually became increasingly sleepy, finally lapsed into coma, and died twelve hours after his admission and fourteen hours after the onset of his illness.

The autopsy findings as they relate to the heart and vessels are as follows (Figs. 1 and 2): The pericardial sac contains no excess of fluid and is free of

adhesions. The heart is moderately enlarged, measuring 11.8 cm. x 12.2 cm. x 5 cm. Together with the great vessels, it weighs 660 gm. The epicardial fat is diminished in amount, and on the anterior surface of the left ventricle near the apex is a tendinous fleck about 1 cm. in circumference. The left ventricle is slightly dilated and moderately hypertrophied, its wall measuring 1.8 cm. to 2.2 cm. in thickness. The right ventricle is moderately dilated and hypertrophied, its wall measuring 0.5 cm. to 0.7 cm. in thickness. The right auricle is markedly dilated and filled with ante-mortem thrombi. The valves are negative except for a dilatation of the tricuspid ring and slight thickening of the corpora arantii of the aortic cusps. The heart muscle is yellowish-brown in color and somewhat friable.

Arising from the aortic arch by a wide mouth, is a saccular aneurysm, the size of an orange. The sacculation commences 3 cm. above the aortic ring and extends

Fig. 2.—Arteriovenous aneurysm, posterior view.

to the right and posteriorly. From the base of the aneurysm, there projects a shallow secondary sac, the size of a walnut. Its wall is very thin and translucent and exhibits, approximately in its center, a circular perforation 0.4 cm. in diameter. The edge of the perforation is ragged and hemorrhagic and a probe passed through it enters the superior vena cava. The floor of the aneurysm proper is covered with reddish-gray thrombi. The intima of the thoracic aorta is greatly altered. It is cloudy, thrown into irregular folds and furrows and shows numerous hyaline, translucent, slightly raised nodules. The coronary arteries show some narrowing of their orifices and a few atheromatous plaques in the left anterior descending branch near its origin.

The superior vena cava is markedly dilated and intimately adherent to the aneurysm. The perforation is situated 2 cm. above the termination of the vein in the right auricle and 1.5 cm. above the opening of the vena azygos. It is slightly smaller than on its aortic aspect. The intima of the superior vena cava exhibits no other abnormalities.

Microscopically, the heart muscle shows hypertrophy, marked edema, slight interstitial fibrosis and moderate hyaline and fatty degeneration of the muscle fibers. The aorta is the seat of a typical luetic mesaortitis. Miliary gummata are present about the vasa vasorum, and the greatly scarred media are invaded by this cellular granulation tissue, which often surrounds necrotic foci. The intima is thickened and hyaline.

Sections near the perforation reveal the wall of the aneurysm to be composed of hyaline fibrous tissue, covered with a thin layer of hyalinized thrombus. The adventitia is profusely infiltrated with round and plasma cells and an occasional multinucleated giant cell. The wall of the vein is sparsely infiltrated with round and plasma cells. As the perforation is approached, both walls become increasingly edematous and more markedly infiltrated with inflammatory cells, mostly polynuclear cells. Large necrotic foci appear in the wall of the aneurysm surrounded by these inflammatory cells. Finally, at the site of perforation the walls are completely necrotic and densely infiltrated with polynuclear cells, many of the latter being in various stages of degeneration and disintegration. All the changes described are much more pronounced in the artery than in the vein.

COMMENT

We do not wish to enter into an elaborate discussion of the many interesting phases of this condition, but we cannot refrain from enumerating briefly the cardinal diagnostic criteria which this typical case demonstrates so well. They are:

1. Evidences of obstruction to the circulation of blood in the superior vena cava and its tributaries: cyanosis, edema, coldness and distention of the veins.
2. The suddenness of the onset of these symptoms.
3. Evidence of a tumor in the thorax and the probability that it is aneurysmal in nature.
4. The existence of a murmur characteristic of a communication between an artery and a vein, that is, a continuous one intensified by systole.

Not all these criteria are always present, and they may be greatly modified, but a typical case such as this not only offers no diagnostic difficulties but remains forever indelibly impressed on the memory.

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TWO-TO-ONE RIGHT BUNDLE-BRANCH BLOCK

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CHARLOTTE, N. C.

TWO-TO-ONE right bundle-branch block is a rare phenomenon that has been reported only once.[1] It consists of a normal sino-auricular rhythm with the alternation of normal and abnormal ventricular complexes, the abnormal complex exhibiting right bundle-branch block.

In 1928 Leinbach and White published a report of their case which progressed to complete right bundle-branch block within a period of five days. The first electrocardiogram showed a pure two-to-one right bundle-branch block, the second showed the same phenomenon, but with contiguous blocked impulses occurring once; the third, complete block of the right bundle of His. Included in their report were tracings obtained by Dr. Stenstrom of Sweden in which this phenomenon occurred as a brief event of a few beats' duration between relatively normal bundle-branch conduction and complete right bundle-branch block. In the latter case exercise with increase in the heart rate impaired intraventricular conduction, while slowing of the rate by vagal pressure restored normal conduction.

Baker[8] has described a temporary bundle-branch block occurring during tachycardia, with restoration of normal intraventricular conduction as the heart rate became slower. The administration of oxygen raised the threshold for defective conduction so that the normal complexes persisted in spite of an increase in rate that previously had produced the block. Electrocardiograms have been published illustrating variations in degree of block or even alternating right and left bundle-branch block, but except for the two cases cited by Leinbach and White the two-to-one phenomenon has not been observed.

An additional case of two-to-one right bundle-branch block is reported here. The patient was referred for an electrocardiogram by Dr. Lucius G. Gage of Charlotte, when he noticed on physical examination a striking alternation of the first heart sounds, one being clear and ringing, the next soft and muffled. There was no accompanying alternation in blood pressure.

CASE REPORT

Mrs. F. W. White, a primipara, aged 61 years.

Diagnosis: (1) Hypertensive cardiovascular disease; (2) congestive failure; (3) right bundle-branch block.

Complaint: Dizziness, palpitation.

Family History: Father died at 86 years of age following a third cerebral hemorrhage; paternal grandfather died at 86; paternal grandmother at 80; mother died at 66 suddenly of unknown cause; one brother died at 50 of cerebral hemorrhage; two sisters died during operations; one brother and two sisters are living and well.

Previous Medical History: She does not remember any contagious diseases in childhood but did have malaria. She had typhoid fever at sixteen; pneumonia twice in adult life and a tonsillectomy at 57 years. In 1928 she had an illness characterized by tachycardia and vertigo lasting a few weeks. Her systolic blood pressure is reported to have been over 200 mm. of mercury and her pulse 120 at that time.

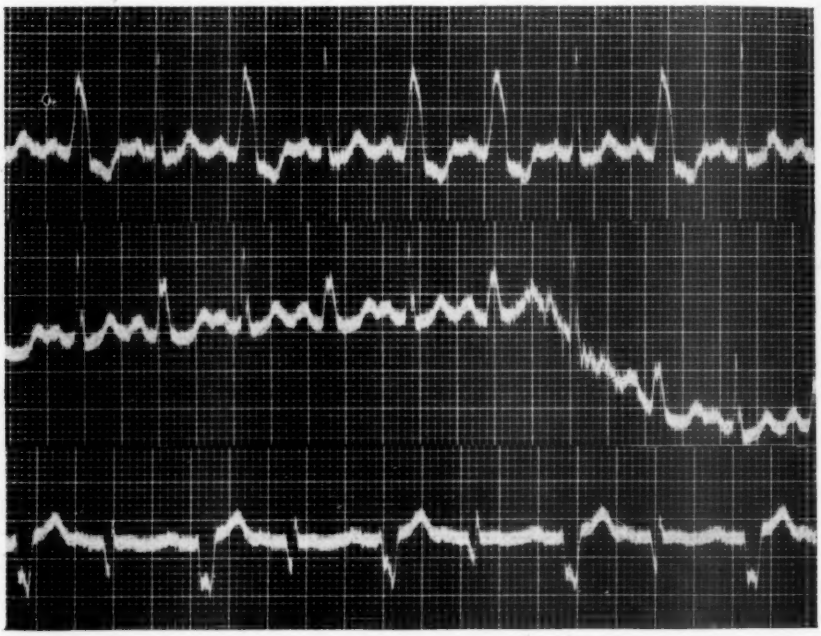

Fig. 1.—Electrocardiogram (Leads I, II, and III) taken April 14, 1930, showing a sinus rhythm, rate 140, and two-to-one right bundle-branch block. Two successive blocked impulses are seen in Lead I. This occurred again in Lead I (not shown) but did not occur elsewhere.

Present Illness: Her present symptoms appeared in the latter part of March, 1930, following an active social life with financial worries of several months' duration; in addition she had been under a mental strain most of her adult life due to marital difficulties. Her first symptoms were transient palpitation, tachycardia, and vertigo following emotional stress. These attacks became more frequent, of longer duration, and in addition she had edema of the ankles, dyspnea on exertion and slight orthopnea.

Physical Examination (April 14, 1930): Showed a well nourished woman of 61 years, mentally alert though apprehensive and irritable.

The eyes, ears, and nose were negative; the tongue was coated, and there was extensive pyorrhea alveolaris. The thyroid gland was not palpably enlarged; there was no exophthalmos or tremor, no enlargement of the cervical lymph nodes.

At the bases of both lungs there were numerous medium moist râles.

Heart: The heart was enlarged to the left, and the rate was rapid, but there were no murmurs. A definite alternation in the first sounds was heard and consisted of a clear ringing sound alternating with a softer muffled sound. This was heard with equal intensity over both the aortic and the pulmonic areas. The systolic blood pressure was 220 mm. of mercury, the diastolic 110 mm.; no alternation in the systolic or diastolic pressure to correspond with alternation in the heart sounds was heard.

The abdomen was pendulous but otherwise negative. The liver and spleen were not palpable.

The skin, the extremities except for slight edema of the ankles, and the reflexes were normal.

Laboratory Data: The urine was acid in reaction with a specific gravity of 1.010 and contained a faint trace of albumin but no sugar, and had no pus, blood,

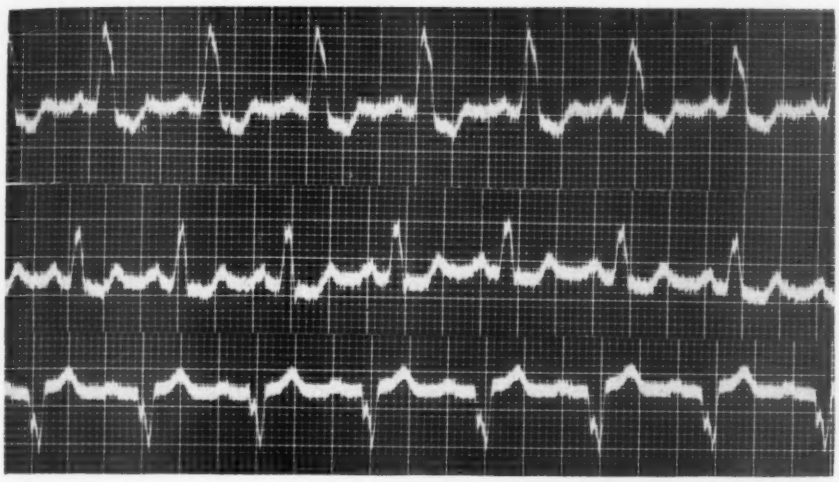

Fig. 2.—Electrocardiogram (Leads I, II, and III) taken April 17, 1930, showing a sinus rhythm and complete right bundle-branch block, rate 105.

or casts in the sediment. The white blood count was 9,900; the red cell count was 5,200,000; the hemoglobin 100 per cent. A few days later the blood sugar four hours after breakfast was 98 mg. per 100 c.c. of blood; the blood urea nitrogen 6.8 mg., the creatinin 1.27 mg. The Wassermann test was negative. Basal metabolism determinations were unsatisfactory, ranging from +8 per cent to +14 per cent, and she refused to attempt further tests.

Electrocardiograms: A tracing (Fig. 1) taken at the time of her first examination, April 14, 1930, shows a sinus rhythm, rate 140, and two-to-one right bundle-branch block save for two instances in Lead I where two successive blocked impulses are seen. A tracing (Fig. 2) taken April 17, 1930, after the patient had taken a total of 10.5 grains of powdered digitalis leaf during the preceding two days, shows a sinus rhythm, rate 105, and complete right bundle-branch block. A third tracing taken May 22, 1930, also shows a sinus rhythm with complete bundle-branch block. Symtomatically she had improved and had failed to return for more frequent observation as requested. Prior to this last tracing she had been taking 1.5 grains of digitalis daily but had voluntarily discontinued the drug four or five days previously.

SUMMARY

A case is reported showing at first two-to-one right bundle-branch block and later complete right bundle-branch block. Only two other instances of this phenomenon have been found in the literature, both being recorded in the same report; one of these was a brief transitional event, the other of longer duration to which the case reported here is comparable.

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CONGENITAL HEART-BLOCK

Report of a Case

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IN DISCUSSING congenital heart-block Maude E. Abbott,[1] in her comprehensive study of "Congenital Cardiac Disease," states that "This is a rare condition, but of great interest from the physiological standpoint and from that of the cardiac anomaly which is nearly always associated." Abbott further states that of the cases reported in the literature, only those having been proved by graphic records and where the history of the block dates back to early childhood, can be considered as cases of congenital heart-block. Of such cases she states there were sixteen in the literature, only one of which, that of Wilson and Grant,[2] having come to autopsy.

The following year (1928) Davis and Stecher[3] published twenty cases of congenital heart-block, nineteen from a review of the literature and one of their own, these cases having been proved by electrocardiograms or pulse tracings.

A year later, Yater[4] working at the Mayo Foundation published thirty cases of proved congenital heart-block, twenty-nine from a review of the literature and one of his own. Of these thirty cases, three came to autopsy—that of Wilson and Grant[2] as already mentioned, that of Perotti[5] and his own.

It is important to note that of the cases proved by graphic records, those studied with the electrocardiograph are undoubtedly the most convincing. When Fulton, Judson and Norris[6] published a paper entitled "Congenital Heart-Block" occurring in a father and two children, one an infant, proving this condition with polygraphic tracings, White, Eustis and Kerr[7] denied their contention, stating that only the infant's tracing showed a true block, whereas the other two polygraphs were normal, yet were not correctly interpreted.

As for the factors responsible for the production of congenital heart-block, it should be mentioned that, in those two of the three cases that came to necropsy, and in which histological studies were made, developmental defects in the auriculoventricular bundle were found and not a prenatal endomyocarditis.

CASE REPORT

History.—Bernard F., a boy, aged fourteen years and eight months old, was recommended to our cardiac clinic at the Crown Heights Hospital on January 14, 1930, by Dr. Louis R. Lang because of an abnormality of the heart, manifesting it-

self by a loud systolic murmur heard over the midprecordium and discovered by him during a casual examination. The boy himself had no symptoms referable to the heart. In fact he complained only of occasional frontal headaches coming on especially after school, not relieved by glasses. He had been a full-term baby, delivered spontaneously, weighed seven pounds at birth, was breast fed until seventeen months of age and never cyanotic. He sat up at six months and showed his first teeth at seven months. He began to walk between eighteen months and two years. His mother, who was both intelligent and cooperative, told us that as a youngster his appetite was very poor and he developed very slowly; at the age of eight years he weighed only 30 or 35 pounds.

This year he changed two of his deciduous teeth and he still has three deciduous teeth left. His past history is absolutely negative for rheumatic fever, chorea, diphtheria, tonsillitis or scarlet fever. He had measles and mumps when seven years of age. When he was four years old, his mother took him to the country. While there, he was taken to a physician because of a slight cold. The doctor at that time asked the mother if she knew there was something wrong with the boy's heart. At present his appetite is good, he sleeps well and his bowels are regular.

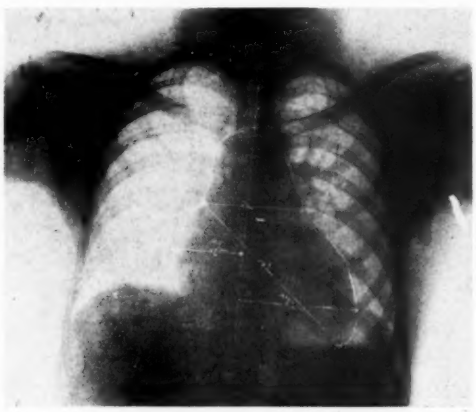

Fig. 1.—Teleroentgenogram. Enlargement of all cardiac diameters indicated by measurements.

He is alert mentally, being in the second year in high school. He was always excused from gymnasium exercise because of the murmur.

The family history is essentially negative, father and mother being well, as is a sister of twenty-two years of age. He lost recently, a brother of twenty-one, of some streptococcus infection—which prompted the mother to have this boy thoroughly examined.

Physical Examination.—The boy was 59¾" tall and weighed 103 lb. His color was good. The fingers showed no cyanosis or clubbing. The pulse rate was 48 per minute, regular and full and corresponded with the apex rate. The apex impulse was in the fifth intercostal space, slightly outside the nipple line. No thrill was palpable anywhere over the precordium. The left border of the heart extended 8.5 centimeters in the fifth space to the left of the midsternal line and right border extended 4.75 centimeters to the right of the midsternal line. A loud systolic murmur was audible over the precordium with maximum intensity in the second and third interspaces, immediately to the left of the sternum. P-2 was slightly accentuated as compared with A-2.

Laboratory Observations.—The urine showed a faint trace of albumin, otherwise was negative. The blood count showed 4,130,000 red cells and 6,000 white cells.

Hemoglobin was 83 per cent (Sahli). A teleroentgenogram and fluoroscopic examination showed an enlarged heart increased in all diameters (Fig. 1) with a slight fullness in the pulmonic region and vigorous pulsations in the region of the pulmonic conus. The cardiothoracic ratio was 58, which is considerably above normal for his age and development. Wassermann reaction was negative and the blood chemistry was entirely normal. His blood pressure was 120 mm. systolic and 65 diastolic.

The electrocardiogram showed complete auriculoventricular dissociation, with tendency to right ventricular preponderance. The auricular rate was 83 per minute, and the ventricular rate was 48; both were regular (Fig. 2).

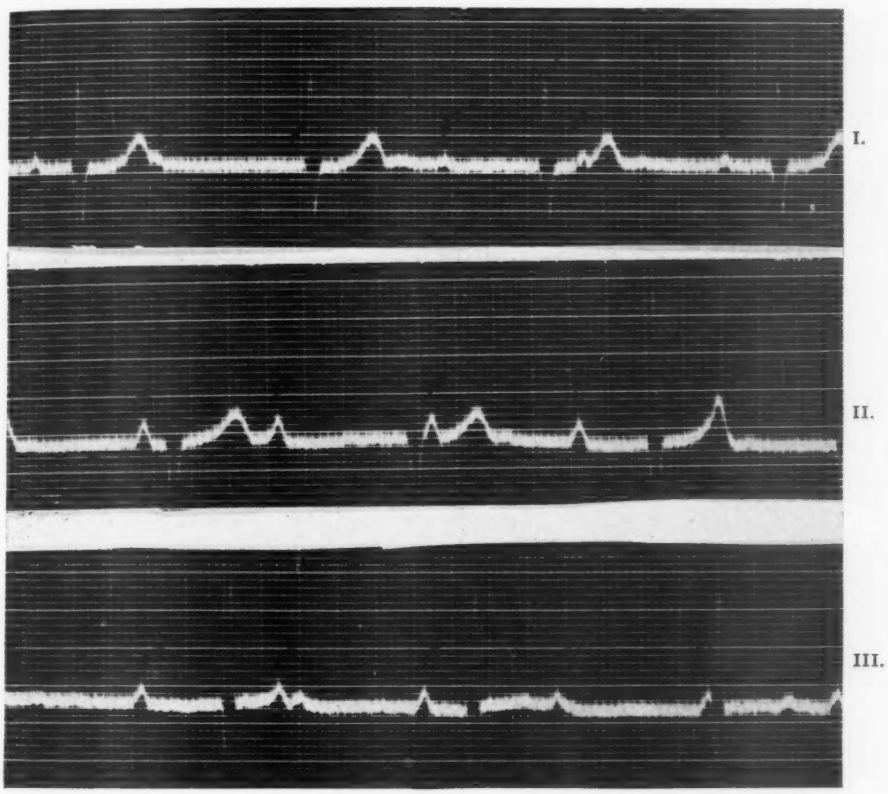

Fig. 2.—Electrocardiogram, Leads I, II, III. Complete auriculoventricular dissociation with tendency to right ventricular preponderance.

Clinical Course.—We reexamined him on February 1, 1930, and again on March 15, 1930, and on both occasions he showed a pulse rate under 50, exercise (jumping first on one foot and then on the other for three minutes) having no effect upon his pulse rate. His blood pressure on both occasions was 120 mm. systolic and 65 diastolic. He is still under our observation.

COMMENT

This case bears out previous observations by others, that cardiovascular symptoms, such as precordial pain, dyspnea, palpitation, syncope, cyanosis or clubbing of the extremities are conspicuous by their

absence, despite the complete heart-block. In fact the patient never complained and never had electrocardiograms taken before, although the mother knew he had a murmur and slow heart since early childhood. It was rather his brother's premature death that prompted this examination, with the result that the complete heart-block was incidentally discovered.

Developmental defects usually occur in multiples. In this case heart-block, probably resulting from developmental defect of the bundle, was associated with the retention of the deciduous teeth to a late age.

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Department of Reviews and Abstracts

Selected Abstracts

Cookson, Harold: The Etiology and Prognosis of Auricular Fibrillation. Quart. J. Med. **23**: 309, 1930.

The prognosis in the two largest etiological groups of fibrillation has been studied in a group of thirty-six cases admitted to the London Hospital. The expectation of life is greater in that type which has often been referred to as the arteriosclerotic.

The influence of various other factors also has been considered. In mitral stenosis, cerebral embolism is shown to occur as frequently when the rhythm is normal as when fibrillation is present. When partial block is present apart from treatment, the outlook for patients with fibrillation is better. Fibrillation of the auricle does not appear to add to the gravity of a case in which complete block already exists; when the two disorders are combined, Adams-Stokes attacks have very rarely occurred. The prognosis is adversely affected by bundle-branch block. Premature ventricular contractions occurring spontaneously do not affect it.

The auricular oscillations of the electrocardiogram are generally smaller in the nonrheumatic than in the rheumatic type. There is little evidence of any relation between the duration of fibrillation and the amplitude of these waves.

Angina of effort, coexisting with fibrillation, was discovered five times in 2,000 patients with fibrillation. In coronary thrombosis the advent of fibrillation may or may not relieve the pain; relief seems more likely if congestive failure results.

Infective endocarditis and auricular fibrillation are both by themselves common sequelae of rheumatic carditis, but are very rarely combined. Death is not infrequently sudden in auricular fibrillation.

Schwentker, Francis F., and Noel, William M.: The Circulatory Failure of Diphtheria. III. The Treatment of the Circulatory Failure of Diphtheria. Bull. Johns Hopkins Hosp. **46**: 359, 1930.

It is believed that in diphtheria intoxication there is a profound disturbance of carbohydrate metabolism. The disturbances following this intoxication usually become evident first in deficiencies in the circulatory mechanism, since this set of tissues can never be placed entirely at rest.

The authors suggest that carbohydrate in the form of dextrose be supplied to combat this disturbance. They have treated 14 patients with intravenous injections of dextrose. All of these patients were of the group showing signs of circulatory failure in the early stages of the disease and were so toxic that death was imminent. In 13 of these cases the patients recovered. In most instances the symptoms were rapidly alleviated; the temperature and pulse rate returned to normal, the toxic condition disappeared and convalescence was uneventful.

The authors recommend that 50 per cent solution of glucose be injected intravenously and that for each ½ grams of glucose one unit of insulin be given intramuscularly. They believe that the power to utilize carbohydrates has been seriously disturbed in these patients and that the insulin is necessary to aid in using the glucose. Additional fluid should be supplied by the subcutaneous or intraperitoneal route, in order not to risk an added load on the failing circulation. These injections could be repeated depending upon the appearance of the patient.

Nye, Robert N., and Parker, Frederic, Jr.: Tissue Reactions in Rabbits Following Intravenous Injection of Bacteria. Am. J. Path. 6: 381, 1930.

The present paper deals with the methods used to produce the lesions in the body following the injection of bacteria, also a detailed description of the histological changes, is included.

The authors have found that following the intravenous injection of relatively large doses of various dead bacteria into rabbits there is a marked reaction of the tissue which contains cells of the reticulo-endothelial system. This reaction consists in an increase of lymphoid cells which are eventually transformed into, or replaced by, monocytes and giant cells. Such lesions ordinarily are temporary and result in no permanent damage. Identical lesions occur after the intravenous injection into rabbits of various colloidal substances.

They believe that such changes represent the reaction of normal rabbits to the disposition of foreign materials in the blood stream and have nothing to do with reactions secondary to sensitization or immunization.

Clawson, B. J.: Experimental Streptococcic Inflammation in Normal, Immune and Hypersensitive Animals. Arch. Path. 9: 1141, 1930.

Experimental streptococcic inflammatory lesions were studied by both gross and microscopic examination in animals under three specific conditions; normal, immune, and hypersensitive. The lesions studied were produced by the injection of small doses of streptococci into the subcutaneous tissues of rabbits.

The first group of normal animals had not had any previous injection and showed no agglutinins for streptococci at the time of the multiple subcutaneous injections. The second group of animals which had been given an immunized dose of streptococci intravenously showed agglutinins in the blood and some at the time of the secondary injections. The third group consisted of animals which had received one subcutaneous injection of agar of 45° C., heavily seeded with streptococci. Agglutinins in the blood of most of these animals were absent at the time of the secondary multiple subcutaneous injections and low at the time when the animals were killed. These animals were called the hypersensitive animals.

Experimental subcutaneous nodules with a polyblastic type of inflammation, similar to those seen in cases of human rheumatic infection can be produced in normal immune and hypersensitive animals by regulating the dose of the injection. These nodules can be produced with much smaller doses in the hypersensitive animals.

General immunity tends to retard the development of subcutaneous nodules except in cases in which the subcutaneous injections are made in from seven to twelve days after the primary immunizing inoculations.

The relationship between allergy and the pathogenesis of experimental rheumatoid subcutaneous nodules appears to be quantitative only.

Valentine, Eugenia, and Van Meter, Martha: The Localization of Streptococci in the Tissues of Rabbits. J. Infect. Dis. 47: 56, 1930.

In this investigation the lesions produced in rabbits following the injection of streptococci secured from the mouths of clinically healthy persons have been studied. Specimens from the tonsils and teeth of persons with evidence of focal or systemic infection were used for comparison. The ability of streptococci from these human sources to invade the tissues of rabbits following intravenous inoculation and to produce local pathological processes has been borne out and cultures especially of the alpha or green producing variety frequently localized in the joints and at times (13 per cent) in the heart, kidneys and other tissues regardless of the clinical

history of the person who furnished the specimens. There is some indication that these green producing streptococci have a greater invasive capacity for rabbits than other strains and produce heart lesions more frequently.

On the basis of this investigation, there is a tremendous variation in attempts to correlate the localization of streptococci in rabbits with the sources of the cultures. It does not appear that the ability of strains to localize is an inherent quality of the organisms associated with similar foci in the human host. It is not apparent what factors govern specific localization.

Derick, C. L., Hitchcock, C. H., and Swift, Homer F.: Reactions of Rabbits to Non-Hemolytic Streptococci. III. A Study of Modes of Sensitization. J. Exper. Med. **52**: 1, 1930.

The most satisfactory method thus far found for the induction and maintenance of a high degree of hypersensitivity against nonhemolytic streptococci consists in the repeated production of small focal lesions with minimal doses of bacteria. The authors have studied the method of producing agar foci of infection in rabbits, in order to simulate conditions occurring in humans in relation to rheumatic fever. They believe that after a preliminary sensitizing period of about two weeks' duration with either large initial or small multiple daily inoculations, the later foci need be produced only at seven to ten day intervals.

Harrison, Tinsley R., and Pilcher, Cobb: Studies in Congestive Heart Failure. II. The Respiratory Exchange During and After Exercise. J. Clin. Invest. **8**: 291, 1930.

Under basal conditions the individuals with congestive cardiac failure who were studied had increased ventilation, but their metabolic rates were usually normal. Exercise which produced no discomfort in normal subjects caused distress in the patients, and the degree of distress was usually proportional to the amount of edema. The ventilation increased more in the patients. The oxygen intake during the exercise was usually somewhat less and the oxygen debt correspondingly greater than in normal subjects. The total oxygen requirement was usually not changed. The excess carbon dioxide production during the exercise was often slightly greater, and immediately after the exercise it was usually considerably greater than in normal subjects. The patients with the most edema had the greatest carbon dioxide excretions.

The maximal exercise of which decompensated patients were capable was much less than for normal men. Maximal values for oxygen intake during exercise and for oxygen debt were much less in the patients than in the normal subjects. Maximum ventilation was also less. One cardiac patient who had never been decompensated on performing maximal exercise had an oxygen requirement and oxygen debt comparable to those of normal individuals but had a ratio of oxygen intake during exercise to oxygen debt comparable to that of the decompensated patients. One patient with mitral stenosis and only slight edema had a lower oxygen intake and carbon dioxide excretion during exercise than any other subject studied.

From these findings the following conclusions are drawn:

Subjects with mitral stenosis and only slight edema may suffer primarily from inability to increase their cardiac output per minute.

Subjects with edema and hypertensive heart disease may suffer from (a) a low maximum cardiac output; (b) impairment of oxygen utilization, so that with a given cardiac output per minute the oxygen intake is less; (c) diminished buffering power of the tissues.

In patients who have had edema of severe degree for a long time, the limiting factor, in so far as gas exchange is concerned, does not appear to be decreased oxygen intake but inability to acquire a large (normal) oxygen debt, and this discrepancy is believed to be due to impairment of tissue buffering power.

Pilcher, Cobb, Clark, Gurney, and Harrison, Tinsley R.: Studies in Congestive Heart Failure. III. The Buffering Power of the Blood and Tissues. J. Clin. Invest. **8:** 291, 1930.

The P_H and carbon dioxide content of the blood of normal subjects and of patients with congestive heart failure has been studied before and after (a) administration of large doses of ammonium chloride, (b) breathing 5 per cent carbon dioxide and (c) a standardized exercise.

The findings in patients with heart failure at rest were usually within normal limits, but a state of acidosis was found in three patients with very severe symptoms. The changes occurring after administration of ammonium chloride and after breathing carbon dioxide were usually within normal limits in patients with congestive failure. The changes in P_H after exercise were usually greater in decompensated patients than in control subjects, and the degree of change was, with one exception, proportional to the extent and duration of the edema. This is believed to be compatible with the presence of diminished buffering power of the tissues in heart failure.

One compensated cardiac patient showed changes similar to those found in control subjects and one patient with noncardiac edema showed changes similar to those in the decompensated patients. This suggests that edema itself may be related to changes in the tissues of patients with heart failure.

Harrison, Tinsley R., Pilcher, Cobb, and Ewing, George: Studies in Congestive Heart Failure. IV. The Potassium Content of Skeletal and Cardiac Muscle. J. Clin. Invest. **8:** 325, 1930.

The potassium content of the skeletal and cardiac muscle of individuals dying of congestive heart failure was found to be less than that of subjects dying without edema. The potassium content per unit of dry weight of edematous muscle was less than that of nonedematous muscle. This was true whether the edema was due to heart disease or not.

The suggestion is offered that loss of potassium with consequent diminution in the buffering power of the heart muscle constitutes a physicochemical factor in the production of "cardiac fatigue." In patients with congestive cardiac failure the decrease in potassium is believed to have been originally an effect of heart failure, but is considered as probably a secondary but important cause of subsequent breaks in compensation.

Pilcher, Cobb, Calhoun, J. Alfred, Cullen, Glenn E., and Harrison, Tinsley R.: Studies in Congestive Heart Failure. V. The Potassium Content of Skeletal Muscle Obtained by Biopsy. J. Clin. Invest. **9:** 191, 1930.

The water content of pieces of gastrocnemius muscle removed by biopsy from patients with cardiac edema was invariably increased. The percentage of solids was correspondingly decreased. These changes usually persisted after clinical signs of edema had disappeared. The potassium content of the wet muscle from edematous patients was invariably abnormally low. The amount of potassium in the dry muscle was usually but not always diminished. As edema decreased, the potassium content of the wet muscle rose in three subjects; that of the dry muscle increased in two of them.

The administration of potassium dibasic phosphate was followed by a rise in the potassium content of the muscle.

Blumgart, Herrman L.; Gargill, Samuel L.; and Gilligan, Dorothy Rourke: Studies on the Velocity of Blood Flow. XIV. The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis. J. Clin. Invest. **9**: 91, 1930.

Sixteen series of measurements were made in 7 patients with myxedema in order to correlate the clinical manifestations with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs.

In each patient measurements when the basal metabolic rate was low were compared with subsequent measurements when the basal metabolic rate had been elevated to normal by appropriate doses of thyroid gland by mouth. The plasma volume per kilogram of body weight was low and tended to increase on administration of thyroid gland.

The pulse rate was low and bore a rough relationship to the basal metabolic rate. As the metabolism rose, the pulse rate approached normal. The venous pressure was within the normal limits of normal in all 7 patients.

The vital capacity of the lungs was strikingly diminished in all subjects in the absence of any signs of congestive heart failure and did not show significant change following treatment. The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate.

The respiratory minute volume was decreased before treatment and always rose significantly as the basal metabolic rate increased. The velocity of blood flow was strikingly slow in every subject and corresponded closely with the degree to which the metabolic rate was lowered. After taking thyroid gland by mouth, the rise in the metabolic rate and the increase in the velocity of blood flow to normal took place simultaneously and closely paralleled each other.

The slowing of blood flow in myxedema was almost as great as that observed in patients with rheumatic valvular heart disease with auricular fibrillation and symptoms and signs of congestive failure. None of the myxedematous patients showed clinical evidences of cardiovascular disease.

The great increase in velocity of blood flow and the consequent increased cardiac work that occurs when the basal metabolic rate is raised to normal affords a rational explanation of the clinical manifestations of cardiac insufficiency which occur not infrequently following thyroid gland therapy in myxedema.

The changes in the pulse rate, basal metabolic rate and velocity of blood flow in myxedema are compared to those previously reported in thyrotoxicosis. The comparison indicates that the increased velocity of blood flow in thyrotoxicosis results from the increased basal metabolic rate rather than from a specific toxic effect on the heart.

The findings emphasize the close interrelation between blood flow and metabolism and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates.

Blumgart, Herrman L., Gargill, Samuel L., and Gilligan, Dorothy Rourke: Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis. J. Clin. Invest. **9**: 69, 1930.

Twenty-seven series of measurements were made in thirteen patients with thyrotoxicosis in order to correlate the clinical manifestations with changes in the velocity of blood flow through the lungs, the basal metabolic rate, pulse rate, venous

and arterial pressures and vital capacity of the lungs. Measurements made when the basal metabolic rate was elevated were compared with subsequent measurements when the rate was reduced.

There was a general but inexact relation between the degree of elevation of the pulse rate and the increase in the basal metabolic rate. No significant deviations from the normal were observed in the venous blood pressure before or after treatment. Diminution in the vital capacity of the lungs was an inconstant finding. With a decrease in the basal metabolic rate, the vital capacity of the lungs tended to increase.

The velocity of the blood flow was strikingly increased so that the pulmonary circulation time was the fastest yet recorded in man. The increase in velocity of blood flow through the lungs was proportional to the degree of elevation in the basal metabolic rate. This emphasizes the strain under which the heart labors in thyrotoxicosis.

In nine patients with thyrotoxicosis but without circulatory failure, the basal metabolic rate averaged 33 per cent above the normal, while the velocity of blood flow through the lungs averaged 83 per cent above the normal. In 4 thyrotoxic patients with similar basal metabolic rates but with cardiovascular disease, the velocity of blood flow was slightly slower. The fact that the latter group of patients experienced dyspnea on slight exertion emphasizes the close interdependence of the circulatory-respiratory-metabolic mechanism. When the basal metabolic rate was lowered by the administration of compound solution of iodine or by operation, the velocity of blood flow was correspondingly slowed.

Morton, John J., and Scott, W. J. Merle: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities. J. Clin. Invest. 9: 235, 1930.

The importance of deciding whether a given peripheral vascular disease is due to vasospasm, occlusion of the lumen, or a combination of the two is recognized. Spinal anesthesia is offered as a test which will simplify the differentiation of these elements in the lower extremities. By its use the vasoconstrictor activity can be accurately measured by the rise in the surface temperature of the feet. The test is simple, safe, rapid, and localized to the part under study.

Under inhalation anesthesia surface temperatures show rapid changes in normal individuals and offer a possibility for a simple test for vascular lesions of the upper extremities.

Brown, George E.: Observations on the Surface Capillaries in Man Following Cervicothoracic Sympathetic Ganglionectomy. J. Clin. Invest. 9: 115, 1930.

Quantitative studies on the capillaries of the skin of human beings have been made both before and after cervicothoracic sympathetic ganglionectomy. Nine cases of advanced Raynaud's disease, four cases of vasomotor forms of scleroderma, four cases of primary scleroderma, two cases of thromboangiitis obliterans, and one case of arthritis of the hands have been studied.

The operation did not cause dilatation of the capillaries (the usual physiological effect) in any case. On the contrary, there were consistent narrowing of the dilated atonic capillaries in Raynaud's disease and an increase in the number of visible capillaries. This could be explained on the basis of a diminished concentration of a theoretical chemical dilator substance in the tissues.

Following sympathetic ganglionectomy in eight cases of vasomotor and primary forms of scleroderma, there was definite reduction in the caliber of the capillaries. The number of open capillaries for each square millimeter of skin increased.

There was quantitative evidence of arteriolar dilatation and lessened response on the part of these vessels to cold. Clinical improvement of some degree occurred in every case.

In the cases of thromboangiitis obliterans and arthritis, in which the capillaries were of fairly normal caliber and tonus, following operation no change in the width of the capillaries was noted. The intermittent slow flow of cyanotic capillary blood changed to one that was rapid, regular, and of normal color. The number of open capillaries was increased.

The major effect of sympathetic ganglionectomy is exerted on the arterioles. There is a sharp, maintained increase in the surface temperature of the skin of the hand in every case. These studies add some confirmation to the opinions of those who hold to the importance of chemical factors in modifying tonus in the capillaries of the skin of human beings. Chemical control of these vessels seems, under certain conditions, more effective than nervous control.

Brams, William A., and Strauss, Herman A.: The Effect of Amyl Nitrite on the Size of the Heart and the Width of the Aortic Shadow as Determined Roentgenologically. Am. J. M. Sc. **180**: 618, 1930.

The size of the cardiac and the aortic shadow was studied roentgenologically in a series of 21 patients before and after administration of amyl nitrite. The group studied included 6 normal persons and 15 showing clinical evidence of arteriosclerosis with and without hypertension.

The transverse diameter of the heart shadow was reduced after amyl nitrite in 18 of the 21 persons studied. Presence or absence of arteriosclerosis or hypertension seemed to play a minor rôle in these changes in diameter. The width of the aortic shadow was increased in 13 of the 21 patients after amyl nitrite. This result also seemed to be independent of the condition of the peripheral vessels or degree of blood pressure. The changes in the cardiac diameter may perhaps be explained by the decreased content in the heart during diastole because of the rapid rate and displacement of blood into the dilated blood vessels and away from the heart.

Wiggers, Carl J., Theisen, Harold, and Williams, Harley A.: Further Observations on Experimental Aortic Insufficiency. II. Cinematographic Studies of Changes in Ventricular Size and in Left Ventricular Discharge. J. Clin. Med. 9: 215, 1930.

The changes in ventricular areas before and after production of an experimental aortic insufficiency were studied at constant heart rates, for the purpose of evaluating the percentile regurgitation. Successive photographs of the exposed heart, properly suspended in the pericardium, were taken at intervals of 0.031 second by means of a moving picture camera. Each photograph was subsequently projected, its outline drawn and the area measured. The values so obtained were plotted as curves and related to simultaneous records of aortic pressures and anteroposterior movements of the left ventricle. The advantages of the method and the precautions necessary in its employment are analyzed in detail.

The curves of outline changes during systole and diastole resemble volume curves in their general characteristics, but do not permit direct conclusions as to the degree to which the stroke of the left ventricle increased during aortic insufficiency. This is accomplished by applying Skavlem's formula, determining the increase in output and adding this to one-half the output of the two ventricles. By taking the left ventricular discharge so determined as a base, the percentile increase in stroke volume is easily calculated.

The results show that during aortic insufficiency the diastolic size is larger and the left ventricular discharge is increased from 16 to 58 per cent in different experiments, on an average 36.4 per cent. Factors other than heart rate and size of leak are responsible for the variations.

In the discussion it is pointed out that changes in heart size without data concerning the stroke volumes of the left ventricle are of no value in determining the percentile regurgitation, but that the percentile changes in stroke volume of the left ventricle give by inference a fair estimate of the percentile regurgitation.

The conclusion is reached that approximately one-third of the discharge during systole regurgitates through insufficient valves during diastole.

Dock, W., and Tainter, M. L.: The Circulatory Changes After Full Therapeutic Doses of Digitalis, With a Critical Discussion of Views on Cardiac Output. J. Clin. Investigation 8: 467, 1930.

Under experimental conditions in dogs a fall of venous pressure regularly accompanied the diminished cardiac output following a full therapeutic dose of digitalis. The authors believe that this is evidence that the change in blood flow was a result of peripheral and not of cardiac actions of the drug. Following a single therapeutic intravenous dose of digitalis, there was a gradual rise of blood pressure, sometimes sustained during several hours in animals which had not been operated on, and simultaneously there were constriction of the vessels of the skin and intestine and an increase in the volume of the liver and spleen due to hepatic vein constriction and to a pooling of blood in these viscera. These changes must have resulted in the diminished venous return to the heart and a diminished output and heart size.

The authors believe that these facts are in agreement with the generally accepted view that the output of the normal heart is governed largely by the venous return. The work of previous investigators has shown that the heart contracts with increased efficiency after therapeutic doses of digitalis but that the effect on cardiac output varies with the functional state of the circulation. The action of the drug in man probably varies in the same way; i.e., the output of the normal heart is reduced, but in such pathological states as heart failure with passive hyperemia, digitalis would tend to increase the cardiac output and to restore the venous pressure to a normal level.

Tainter, M. L., and Dock, W.: Further Observations on the Circulatory Actions of Digitalis and Strophanthus With Special Reference to the Liver, and Comparisons With Histamine and Epinephrine. J. Clin. Investigation 8: 485, 1930.

When dogs are given by intravenous injection doses of digitalis corresponding to the full therapeutic dose for man, they exhibit a rise in arterial and fall in right auricular pressure but a simultaneous rise in portal vein pressure. These changes are also caused by strophanthus. The fall in systemic and the rise in portal vein pressure are due to constriction of hepatic veins. After the liver was eliminated from the circulation by shunting the portal blood directly into the inferior vena cava or by ligating the arteries which supply the splanchnic area, digitalis or strophanthus did not cause a fall in venous pressure but in several instances raised it and did not cause as marked an elevation of arterial pressure as in the animals with the splanchnic circulation intact. Therefore, the fall in right auricular pressure, after giving digitalis to dogs with the hepatic circulation intact, was due to diminished venous return flow and ultimately to an accumulation of blood in the splanchnic or portal region as a result of obstructed hepatic outflow.

The experimental procedures used to determine the actions of digitalis and strophanthus were controlled by comparisons in the same organism with known

actions of histamine and epinephrine which cause a similar pooling of portal blood through a similar mechanism, the actions being modified, however, by changes in other vessels.

Weiss, Soma, and Ellis, Laurence B.: Circulatory Measurements in Patients With Rheumatic Heart Disease Before and After the Administration of Digitalis. J. Clin. Investigation **8:** 435, 1930.

The purpose of the study presented here was to investigate a number of aspects of the circulation before and after the administration of digitalis in patients who were suffering from chronic rheumatic heart disease and who exhibited approximately the same clinical degree of circulatory failure. Repeated circulatory measurements were performed before and after digitalization in 4 patients with rheumatic heart disease. The patients were comfortable, at rest, exhibited no clinical evidence of congestive failure but showed marked reduction in their functional capacity on attempting any muscular activity.

The vital capacity of the lungs, the average cardiac output per minute and per beat, and the mean velocity of the blood flow were well below the normal. The velocity of the blood flow from the arm to face and the circulating blood volume were normal. While the average rate of blood flow was reduced as the result of heart disease, the exchange of carbon dioxide and oxygen between the capillaries and tissue per unit of the circulating blood volume was increased. The capillary circulation responded with increased efficiency in compensation for the impaired cardiac function.

Although all the patients showed clinical improvement as a result of the administration of digitalis, the cardiac output, the velocity of blood flow, the circulating blood volume, and the vital capacity of the lungs showed no significant changes. Certain aspects of the nature of circulatory failure in rheumatic heart disease are discussed. The evidence presented in this study and previous observations reported in the literature do not support the conception that the rate of blood flow is increased in circulatory failure because of rheumatic heart disease, nor that the beneficial effect of digitalis is manifested by its capacity to reduce the cardiac output.

Gold, Harry, and DeGraff, Arthur C.: Studies on Digitalis in Ambulatory Cardiac Patients. J. A. M. A. **95:** 1237, 1930.

The following observations were made in the adult cardiac clinic of Bellevue Hospital on patients with auricular fibrillation with a view of determining the average daily dose of digitalis necessary to maintain the full therapeutic effects that had been induced when the patient was in the hospital. The authors have found that a much lower "effective concentration" of digitalis in the body suffices to produce full therapeutic effects than is required in the average bedridden patients in advanced congestive failure. They have found that in the ambulatory patient full therapeutic effects as judged by the usual clinical criteria of improvement can be produced by daily repetition of a relatively smaller dose of the drug that can then be continued as the daily maintenance dose without producing toxic symptoms.

It is pointed out that in the average ambulatory cardiac patient there is a wide margin between the minimum dosage that produces full therapeutic results and the maximum that can be tolerated without toxic symptoms. This margin is frequently smaller in patients with far advanced failure, and the latter often require the largest dosage that can be tolerated in order to produce the best results. The authors have developed the practice of using relatively large doses of

digitalis to produce the full therapeutic effects and then relatively smaller daily ones in order to maintain these results for long periods of time. They also believe that the explanation of this action is that the smaller doses are necessary in order to maintain the high "effective concentration" of the drug produced by the larger ones. Evidence has been set forth proving, however, that the "effective concentration" of the drug within the body necessary to maintain the effects is usually much lower than that required to produce them in the beginning.

Hyman, Albert S.: Resuscitation of the Stopped Heart by Intracardiac Therapy. Arch. Int. Med. 46: 553, 1930.

The success of an intracardiac injection procedure for the resuscitation of a stopped heart is apparently due more to the effect of the puncture wound made in the wall of the heart than to the chemical substance injected. The myocardium of the normal asystolic heart rapidly becomes irritable with the onset of anoxemia. Under these conditions any mechanical stimulation may irritate the heart to automatic contraction, and the success of massage and percussion of the heart for resuscitation can be explained on this basis. A puncture wound made by the injecting needle becomes a focus of increased irritability from which a stimulus for myocardial contraction may be developed. First contractions of the heart after injection are always extrasystoles, and the initial extrasystolic arrhythmia may give way quickly to a normal sinus rhythm with prompt recovery on the part of the patient.

However, when the period of anoxemia has been so prolonged or so intense that there is considerable disturbance in the electrodynamic factors controlling myocardial contraction, the initial extrasystolic arrhythmia may persist and may be quickly followed by a rapid sequence of ectopic beats. Such a condition leads to pathological fatigue of the ventricles which may be followed by ventricular fibrillation. Ventricular fibrillation is an extremely hazardous disturbance of the heart and is usually accompanied by immediate collapse of the circulation and death of the patient. This phenomenon explains the secondary collapse of the circulation often seen following what has apparently been a successful resuscitation of an asystolic heart. It is suggested, therefore, that the intracardiac puncture be made into the right auricle instead of into the ventricles as is now practiced. Intra-auricular puncture is not difficult and may be performed by using a slightly curved needle four or more inches long which may be inserted into the third interspace at the right sternal margin. The point should be directed toward the midline and to the patient's back. The distance to the right auricle measures about four inches or less, in children about two inches or less. The author points out that the danger of injuring the larger vessels is not great in this position, since they lie above and below this point.

The auricles are more responsive to mechanical stimulation than the ventricles. A mere prick of the needle may be sufficient to initiate contraction. The region of the right auricle reached by the needle is in general near the sinus node, and extrasystolic contractions arising from this location would spread over a more normal pathway than from any other location.

The sequential development of rapid auricular extrasystolic arrhythmia, auricular flutter, and finally fibrillation may not be of special significance so far as the ventricular output to the circulation is concerned, since the phenomenon of physiological block slows the ventricular rate.

Intra-auricular puncture should be attempted in every case of death that occurs as the result of the asystolic heart. The cases most favorable for resuscitation are those not affected by general or cardiovascular disease. In deaths occurring on

the operating table after hemorrhage, shock, anesthesia or other ill-defined conditions like status lymphaticus, prompt resuscitation may result from this procedure, either alone or combined with other life-saving measures, such as artificial respiration, transfusion, etc. In asphyxia neonatorum, it may be specific in its prompt initiation of automatic contraction of the heart.

The author describes nine cases which have been resuscitated by this method.

Blotner, Harry: Coronary Disease in Diabetes Mellitus. New England J. Med. 203: 709, 1930.

This paper presents a clinical study of 35 fatal cases of diabetes with coronary artery disease. Coronary sclerosis was found to occur in about 45 per cent of all diabetic cases brought to necropsy in the Peter Bent Brigham Hospital. The incidence of coronary disease is greater in diabetics than in nondiabetics, since it occurred in only 21 per cent of the nondiabetic group of patients above the age of forty years who were examined at autopsy.

Ten of the diabetic patients had no symptoms referable to the heart before they entered the hospital for the last time. Twenty-five had more or less significant cardiac symptoms from several months to ten years before they came under observation, but most of them entered the hospital for varying complaints which were not related to the heart. The chief cause of death in 43 per cent of all this series of diabetics was directly attributable to heart disease.

Cardiac infarction caused death in 10 per cent of 77 fatal diabetic cases and in 23 per cent of 35 fatal diabetic cases with pathological evidence of coronary sclerosis. Cardiac infarction is not an uncommon complication of diabetes and may be masked by the clinical picture of diabetic coma. Death from cardiac infarction occurred in three cases shortly after a rapid fall in blood sugar concentration following the administration of insulin.

The authors point out that due importance must be attached to the condition of the circulatory system in order to obtain the best therapeutic result in diabetes. A sudden lowering of the blood sugar concentration by insulin may be dangerous for the elderly diabetic patient with vascular disease; such a patient is likely to have sclerosis of the coronary vessels as part of generalized arteriosclerosis. The sudden lowering of blood sugar level by insulin may induce coronary thrombosis with a fatal outcome.

Kaiser, Albert D.: Results of Tonsillectomy. A Comparative Study of Twenty-Two Hundred Tonsillectomized Children With an Equal Number of Controls Three and Ten Years After Operation. J. A. M. A. 95: 837, 1930.

This is a further report on the study of a large group of children who were tonsillectomized previously and compared with a group of similar children without tonsillectomy. Outstanding benefits from the operation are apparent in influencing the incidence of sore throats over a ten-year period. Substantial benefits are apparent in rendering children less susceptible to scarlet fever and diphtheria. Cervical adenitis is decidedly reduced.

Acute head colds and otitis media are not essentially influenced over a ten-year period. Respiratory infections such as laryngitis, bronchitis and pneumonia not only are not benefited but occasionally occurred more frequently in this group of tonsillectomized children.

First attacks of rheumatic manifestations occur from 30 to 50 per cent less often in tonsillectomized children. The greatest reduction occurs in children tonsillectomized early. Recurrent attacks after tonsillectomy are not benefited at all.

Lennox, William G., and Leonhardt, Erna: The Oxygen and Carbon Dioxide Content of Blood From the Internal Jugular and Other Veins. Arch. Int. Med. 46: 630, 1930.

In a large series of patients the authors have measured the oxygen and carbon dioxide content of the blood from an artery and from various veins. The gaseous content of blood from the femoral vein was found to be the same as that of blood from the cubital vein. In sharp contrast blood from the internal jugular vein was more reduced and blood from the external jugular less reduced than blood from a cubital vein. These statements are true for average values. Measurements for individual patients vary widely.

In a series of 51 patients the average corrected respiratory quotient for blood from a cubital vein was 0.84 and from the internal jugular vein, 0.9. More sugar disappeared from the blood in its passage through the brain than in its passage through the arm. The former of these observations suggests that in the metabolism of the human brain, carbohydrates are unusually important.

Hurxthal, Lewis M.: The Appearance Time of T-Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion. Arch. Int. Med. 46: 657, 1930.

Two cases are reported in which records were obtained before and after coronary occlusion. Case 1 showed upright T-waves in all leads one hour after the onset of the attack, later followed by depression, whereas the record six days before the attack showed an inverted T-wave in Lead I. Case 2 showed a distinct but not diagnostic change one hour and fifteen minutes after onset.

The author points out that single tracings made following acute coronary occlusion may appear normal or if abnormal are of little value unless previous tracings have been taken or later records are obtained. At present one must rely on clinical diagnosis rather than on the electrocardiogram in an emergency in which surgical measures are concerned. It is suggested that electrocardiographic observations be made at more frequent intervals following acute coronary occlusion; such observations may prove of distinct value in diagnosis.

Palmer, Robert Sterling: The Treatment of Essential Hypertension. New England J. Med. 203: 208, 1930.

The author summarizes various treatments that have been proposed for this condition. The astonishing number of favorable reports on the use of a large variety of drugs and other forms of treatment in hypentension is an indication that more rigid criteria for the clinical evidence of a hypertensive effect must be met. The author suggests, therefore, that the following criteria might be useful in the clinical estimation of hypertensive action of any given therapeutic measure. It is only by satisfying some such minimum requirements as these that an adequate clinical evaluation may be made and the results of different investigations may be compared.

(1) Each observation shall consist of at least ten successive determinations of systolic and diastolic pressure at one-minute intervals, the same type of instrument to be used at each observation and the patient to be in the same position.

(2) On the whole, it appears advisable that this type of investigation be carried out, when possible, on ambulatory patients, exposed to the daily nervous excitements which the unhospitalized person must meet. The question of preliminary rest may be optional, provided it be always the same.

(3) Two or more, preferably more, weekly observations shall be made before starting treatment.

(4) A fall in the average of the ten readings at successive visits should be demonstrable after a period allowed for the full effect of the treatment, and this effect should be maintained at two or more further observations. The patient should be under treatment for four to six weeks.

(5) The treatment shall then be omitted and a rise in blood pressure shown after ample time has been allowed for the effect of the procedure to have abated.

(6) Finally, a second hypertensive effect of the treatment should again be demonstrable.

Stieglitz, Edward J.: Bismuth Subnitrate in the Treatment of Arterial Hypertension. J. A. M. A. **95:** 842, 1930.

The author proposes the use of bismuth subnitrate in the treatment of arterial hypertension. He has observed the results obtained in two hundred unselected cases of hypertensive arterial disease and one hundred and twenty cases of hypertension in pregnancy and believes the results are satisfactory. The action of the drug is due to the fact that it is sparingly soluble in the intestinal tract, small amounts of nitrate ions being liberated continuously which on conversion into nitrous oxide by Bacillus coli leads to gradual vasorelaxation.

Weiss, Soma, and Ellis, Laurence B.: The Rational Treatment of Arterial Hypertension. J. A. M. A. **95:** 846, 1930.

The authors believe that in a small proportion of cases the blood pressure will return to normal and the symptoms will disappear either permanently or for a prolonged period of time following the institution of approved methods. Such remission in the case of arterial hypertension may, however, occur spontaneously, and these individuals should live well-regulated lives and be followed carefully. In the second group, there will be some lowering of the blood pressure, although not to a normal level with accompanying subjective improvement, and some checking of the progress of the disease. A third and larger group of patients will show no material lowering of the blood pressure, but their symptoms will be lessened, and they will be enabled to live more comfortable lives. In certain of these by the careful regulation of their mode of living acute cardiovascular accidents will be averted, and to that extent their lives will be prolonged. The remainder, in particular many of the cases of malignant hypertension, will progress inexorably, apparently uninfluenced by therapy, to a fatal termination.

Book Reviews

LA TUBERCULOSE CARDIO-VASCULAIRE. LA COEUR DES TUBERCULEUX. By Adrien Pic, and Leon Morenas. Gaston Doin, Paris, 1930. Pp. 268 of text with 15 figures and 4 color plates.

The text is divided in three parts. Part one opens with an extensive discussion of tuberculosis of the pericardium, then takes up in order tuberculosis of the endocardium, valvular lesions of tuberculous origin, tuberculosis of the myocardium, idiopathic cardiac hypertrophy and its possible tuberculous origin and congenital lesions of tuberculous origin, altogether 131 pages. These various subjects are skillfully handled. The value of pericardiotomy for pericarditis is discussed as a satisfactory method of treatment. A satisfactory discussion of the diagnosis of tuberculous pericarditis is presented, including roentgenographic examination both without, and before and after, air injection in the pericardium. Tuberculosis of the cardiovascular system is not of common occurrence in the United States, though it is occasionally seen and is more often overlooked, either by failure to recognize the tuberculous nature of the pericarditis or by failure to recognize the pericarditis during the course of heart disease or tuberculosis. The condition must occur more frequently in European countries, however, since many case reports are included in this discussion and since it is known that other forms of more extensive and massive tuberculosis occur in continental Europe. This is particularly true of children and adolescents with large mediastinal abscesses, massive pulmonary and bone tuberculosis.

Part two discusses the heart of the tuberculous patient. Two important symptoms shown by these patients, palpitation and tachycardia, and their differential diagnosis are discussed. The physical and anatomical modifications of the heart receive deserved attention. Chapters on cardiac insufficiency in the tuberculous patient and combined heart disease and pulmonary tuberculosis are included.

Part three is concerned with tuberculosis of vessels, both arteries and veins, followed by a general résumé of the place of tuberculosis as compared with other infections of the cardiovascular apparatus. A very extensive and complete bibliography concludes the text. The book is well arranged, the discussions are clear, and complete and satisfactory diagnoses and illustrations aid the reader in following the subject. While the field of usefulness of the book will be limited somewhat by the extent of the subject, it makes a most satisfactory addition to those who are interested and have occasion to observe such patients.

H. McC.

HERZ, PULSATION UND BLUTBEWEGUNG. By Dr. Georg Hauffe. 246 pages, with 9 illustrations. J. F. Lehmanns, Munich, 1930.

Periodically a new volume is added to that small class of books which seek to upset orthodox conceptions in science and to replace them by revolutionary views of supposedly far-reaching significance. The book attempts to do this in behalf of the heart and circulation.

The editorial technic common to such endeavors is followed: Current views are not squarely treated, and the evidence accumulated in their support is lightly

brushed aside by facetious statements. This accomplished, a new hypothesis can easily be made to appear plausible through illogical misapplication of a few irrelevant observations on known physical principles.

Two radically new conceptions are developed:

(1) The rhythmic sequence of the heartbeat is conceived as due to mechanical properties of the elastic cardiovascular system rather than to a speculative upbuilding and discharge of an "inner stimulus." The tempo of the heartbeat is not given by impulses formed in and discharged by the sinus node, but is due to a movement externally transferred from the peripheral circulation to the cardiac muscle. The sinus node receives excitations; it does not initiate them. Initiation of stimuli occurs in the peripheral vessels as a result of vascular changes in sufficiently diffused regions.

(2) The heart and pericardium acting together form a combined force and suction pump operating somewhat after the following manner: Contraction of the ventricles expels blood into the aorta. This would dilate the aorta and raise the pressure during systole, as is commonly believed, but the author claims to have made the discovery that the size of the aorta becomes smaller and the arterial pressure falls during systole. This is explained as follows: Contraction of the ventricles in a pericardial sac of constant size serves to unfold the auricular wall, thereby enlarging its cavities. This creates a suction which draws blood into the auricles. But this is not all. The suction component is propagated peripherally through the veins and capillaries to the large arteries. When, on the other hand, the auricles contract, they fill the ventricle not only by the pressure created within but through the negative extracardiac pressure developed without. Lengthy explanations are given to prove that the feeble auricular contraction can indeed develop powerful effects and that the contractions of the auricular appendage determine the proper direction of the blood stream.

The critical reader who hopes to find the experimental proof for these revolutionary conceptions or even a logical set of arguments in their favor is doomed to disappointment. The theories are apparently based on certain physical experiments and clinical studies of the author. The former comprise the observations—which have apparently escaped all physicists—that increased velocity of flow decreases the diameter of elastic tubes. Furthermore, the author found that with a suitable velocity a rapid series of expansions and constrictions can be produced and made to travel over elastic tubes. By varying the velocity of flow, the frequency of such periodic disturbances can be changed, and even irregularities in rhythm can be inaugurated. These mechanical principles are supposed to be duplicated in the circulation.

The clinical observations seem to consist of the x-ray findings, that augmented minute output and increased blood flow cause a diminution in the aortic shadows and a fall in blood pressure. From this the author apparently leaps to the corollary that the size of the aortic and arterial pressure must decrease during systole. The reviewer has looked in vain for direct proof of this assumption.

The author is modest in his assertion that the work of Harvey is not completely upset by his hypothesis but is merely given a more far-reaching significance.

C. J. W.

THE MECHANISM OF THE HEART AND ITS ANOMALIES. By Emile Geraudel. Translated by Louis Faugères Bishop, Sr., and Louis Faugères Bishop, Jr. Williams and Wilkins Company, Baltimore, 1930.

This monograph is devoted to the presentation of the hypothesis that most of the disturbances of the heartbeat are the result of variations in blood flow within the specialized cardiac tissues. In the early chapters there is an account of the

technic of electrocardiography and a detailed description of the anatomy of the tissues mentioned with special reference to their blood supply.

The sino-auricular node is referred to as the "auriculonector," and the atrio-ventricular node, the His-bundle and its branches, as the "ventriculonector." The author believes that the former controls auricular, the latter, ventricular activity. He does not believe that the ventricles respond to the auricles, but thinks that the normal sequence of auricular and ventricular contraction is dependent upon a coördination of the activities of the two "cardionectors" brought about by the manner in which they are supplied with blood.

All of the common disturbances of the heartbeat are interpreted in terms of the hypothesis referred to. The evidence offered in support of this view is meager and unconvincing.

As an example of the views expressed regarding these disturbances, consider the following explanation of the abnormality of the ventricular complexes written by ventricular extrasystoles. Ventricular extrasystoles are premature beats but not ectopic beats; all ventricular beats originate within the "ventriculonector." In certain cases a premature beat is associated with a deformed complex because it occurs at a moment when the myocardium is not "normally relaxed." "The ventricle in particular, the cavity most often interested, is surprised *in flagrante delictu* by the activity of the cardionector affecting it again and prematurely, and its new contraction will not be 'harmonious.'" Few will find this explanation preferable to the one now generally accepted.

The book may be recommended highly in some respects. It is excellently bound, and is printed in large clear type, on very good paper. The electrocardiograms are well reproduced; they are all legible, and all appear to be right side up. It seems fortunate that the book has been published in a limited edition. The appearance of the title page would seem to imply that the translating of a book is a much more important task than the writing of it.

F. N. W.

CLINICAL FEATURES OF HEART DISEASE. By Leroy Crummer, M.D., Emeritus Professor of Medicine, University of Nebraska. 415 pages, Paul B. Hoeber, Inc., New York, 1930.

In the second edition of this book the scope has been somewhat broadened by the addition of chapters on "rheumatic endocarditis" and "subacute bacterial endocarditis." The book remains essentially a clinical presentation, with emphasis on certain personal views of the author which in some instances have not yet gained universal acceptance. On the whole, however, it is an interesting and instructive volume which deserves the popularity it seems to have attained.

T. S. H.